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Geneva, 15–19 November 1993

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1. Introduction

The WHO Expert Committee on the Use of Essential Drugs met in Geneva from 15 to 19 November 1993. The meeting was opened on behalf of the Director-General by Dr F.S. Antezana, Assistant Director-General, 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 required no modification or merely bringing up to date. The eighth Model List of Essential Drugs will be found in section 16 of this report, and explanations of the changes in section 17. The Committee agreed to annex to its report the report of a WHO consultation on the provision and dissemination of drug information (Annex 1), together with guidelines prepared by various WHO consultations on antimicrobial susceptibility testing (Annex 2) and on good clinical practice for trials on pharmaceutical products (Annex 3) in order to bring them to the attention of those in charge of national drug policies.

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 and rational use 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 six further reports (*3, 7–11*).

In undertaking a further review of the list at its present meeting, the Expert Committee was 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 drew 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. The Committee was informed that a WHO Expert Committee on National Drug Policies would be convened in 1994 to review the guidelines for developing national drug policies (*12*).

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

1. A standing committee of health care professionals should be appointed to give technical advice to the national 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 until such individuals can be trained. The first task of the committee should be to recommend a list of essential drugs for the national programme. The committee should remain a part of the national programme for essential drugs, continually advising on matters of technical importance.
2. The international nonproprietary (generic) names for drugs or pharmaceutical substances (*13*) should be used whenever available, and prescribers should be provided with a cross-index of nonproprietary and proprietary names.
3. Concise, accurate and comprehensive drug information should be prepared to accompany the list of essential drugs, in the form of a prescriber's formulary to serve as a pocket guide to rational drug use. More detailed information about drugs should be made available at drug and poison information centres, pharmacies and all educational institutes concerned with training health professionals.
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 and trained personnel for such research must be provided. Clinical trials on pharmaceutical products should follow the Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products included as Annex 3.
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 of the Committee's previous report (*3*). 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.

Because of differing views on the definition of an essential drug in terms of what is meant by the "health care needs of the majority" of the population, the model list has been gradually expanded since its introduction. Some drugs are included that are essential only if a

therapeutic programme is planned to address the diseases for which these drugs are used. For example, the cytotoxic drugs (section 8.2 of the model list) are essential only if a comprehensive cancer treatment programme is planned. Such a programme requires adequate hospital, diagnostic and clinical laboratory facilities for its implementation. In contrast, the drugs used in palliative care (section 8.4) are always essential, even when a comprehensive cancer treatment programme does not exist.

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.

For certain drugs with short half-lives that are rapidly metabolized, such as carbamazepine, calcium-channel blockers and theophylline, conventional-release dosage forms must often be taken three or four times a day to maintain drug levels in the required narrow range. Sustained-release dosage forms can reduce the frequency of drug administration, thereby improving compliance and, often, the therapeutic effectiveness of the drug by maintaining a more constant drug level than can be obtained using traditional dosage forms. Because the preparation of sustained-release products is difficult and requires special expertise, a proposal to include such a product in a national list of essential drugs should be justified by adequate documentation.

5. Quality assurance

Quality assurance of drugs, as embodied in product development, 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-third reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (*14-21*).

Priority should be given to ensuring that the available drugs have been made according to good manufacturing practices (*20*, Annex 1) 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.

The Committee emphasized the importance of WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, particularly in countries with inadequate laboratory facilities for drug analysis which may be unable to carry out the process of quality control. This scheme 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, to provide for a more comprehensive exchange of information between governments (*22*). 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 of a pharmaceutical product can result in treatment failure just as readily as can a deficiency of active ingredients in the product. The bioavailability of essential drugs should therefore 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* (*23*), 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 (*17*). 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. Where national capacity is lacking, a regional effort involving several countries may be useful. In this context, attention is

also drawn to the WHO publication *Basic tests for pharmaceutical substances* (*24*), 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 (*25*) specified in the Model List of Essential Drugs, together with additional information on bioavailability, stability and recommended packaging and storage conditions.

6. Reserve anti-infective agents and monitoring of 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 (*26, 27*). 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. Cefalosporins should be used only to treat specific infections that are resistant to antimicrobials on the main list; for this purpose, they are considered essential. Some are suitable for the treatment of *Haemophilus influenzae* type b meningitis, where there is evidence that strains are resistant to chloramphenicol and benzylpenicillin, or pneumococcal meningitis, where penicillin-resistant pneumococci are common. Ceftriaxone and cefixime are specifically recommended for use in control programmes for sexually transmitted diseases for the treatment of drug-resistant strains of gonorrhoea and chancroid. For example, a single intramuscular dose of 250 mg of ceftriaxone will cure both of these diseases. However, this drug 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. Ceftazidine is an example of a cefalosporin that is used for the treatment of *Pseudomonas aeruginosa* infections resistant to piperacillin and gentamicin.

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 ampicillin, chloramphenicol, sulfamethoxazole/trimethoprim, tetracyclines and nalidixic acid.
- 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 usually resistant to all β-lactam antimicrobials and 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.

In some countries, strains of *Plasmodium falciparum* have developed resistance to all of the antimalarial drugs except for artemisinin and its derivatives. For patients with falciparum malaria resistant to chloroquine, sulfadoxine/pyrimethamine, mefloquine or quinine with tetracycline, the use of artemisinin and its derivatives appears essential. In order to limit

the development of resistance to these drugs and keep them effective for as long as possible, their use should be restricted to areas in which multidrug-resistant falciparum malaria exists. In such countries artemisinin and its derivatives should be used for the treatment of uncomplicated infections resistant to all other antimalarials, or for severe falciparum malaria where quinine is ineffective.

7. Antiviral drugs

Antiviral drugs were 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 cost, none of those currently available was considered to qualify for inclusion in the model list at this time. Aciclovir was, none the less, accepted as being of value in the treatment of severe herpes infections. Similarly, zidovudine was acknowledged to suppress the progression of human immunodeficiency virus (HIV) infection temporarily. Neither was considered essential, however, for the reasons given above.

8. 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 disease control programmes in WHO, international and nongovernmental organizations throughout the world and 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 (*28*), designed to cover the basic needs of a population of 10000 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.

9. 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.

9.1 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.

9.2 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.

9.3 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.

9.4 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.

10. 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.

In 1988, the United States Committee for Refugees (*29*) estimated that more than 30 million people were 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.

10.1 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 over 6 months of age at the first contact and every 4-6 months thereafter according to guidelines published by WHO (*30*, *31*). Priority should be given to severely malnourished children. For infants under 6 months of age, vitamin A supplementation is indicated only for those with measles or eye signs suggesting vitamin A deficiency. For pregnant women, vitamin A supplementation is indicated only for those in high-risk communities, who should receive frequent low-dose supplements where feasible. However, a supplement should be given to all women 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.

10.2 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 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 of time, a routine immunization programme should be started as soon as possible. This should include all seven childhood vaccines currently recommended by WHO, as listed in the WHO document *Immunization policy* (*32*). It is essential that a fully operational cold chain is in place before immunization begins. Guidance on its establishment can be found in *Immunization in practice – a guide for health workers who give vaccines* (*33*). Immunization against diseases other than those recommended above (e.g. meningococcal disease or typhoid fever) should be undertaken only if justified by surveillance data.

10.3 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 (*34*) that at least 15-20 litres of clean water are required per person per day.

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* (*35*). 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 (*36*). Emphasis should be placed on the use of oral rehydration therapy. The use of antidiarrhoeal preparations should be discouraged. Antiemetics should not be used in the treatment of children with acute diarrhoea, and 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 vaccine is of no value; indeed, its use in this situation may create a false sense of protection, which may promote the spread of this disease.

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* (*37*).

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.

10.4 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 8 (*28*) 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 (*20*, Annex 3) 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.

10.5 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 stocks 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, HIV infection and sexually transmitted infections, as well as programmes for maternal and child health care, including family planning.

11. 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 population 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 of 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.

Many drug regulatory authorities have recognized the value of post-marketing drug surveillance and the need for sustained international surveillance schemes. For many years the WHO Collaborating Centre on International Drug Monitoring has collated the reports of national monitoring schemes based on spontaneous notification by health professionals. Originally the programme included only countries with highly evolved drug regulatory agencies, where its main use was for generating signals of possible adverse drug reactions and for confirming cases. Currently the Collaborating Centre is attracting many developing countries which are in the process of establishing national drug policies. WHO is collaborating closely 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 studies using such methods 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 emphasized 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.

12. 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.

12.1 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.

12.2 Clinical and epidemiological aspects

1. Development of facilities and expertise to carry out clinical trials according to the guidelines provided in Annex 3 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.
2. Development of expertise to carry out drug utilization studies and to assess therapeutic practice.

12.3 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 educational and training programmes for prescribers and other health care professionals.
4. 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.

13. 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 (INNs), whose activities have led to the publication of names for roughly 6200 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 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.

On the basis of the Committee's previous recommendations concerning trade-marks derived from INNs, a resolution on nonproprietary names for pharmaceuticals (WHA46.19) was adopted by the World Health Assembly in 1993 (*38*).

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.

14. 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* (*39*), *Drugs used in parasitic diseases* (*37*), and *Drugs used in mycobacterial diseases* (*40*), have already been published. The fourth title, *Drugs used in sexually transmitted diseases and HIV infection* (*41*), is in press, and 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 urged that this activity receive high priority within both WHO and its Member States and that the distribution of the information be as wide as possible. Guidelines on the provision and dissemination of drug information have recently been prepared by a WHO consultative group (Annex 1).

Health care professionals should receive education about the use of drugs not only during their initial professional training but throughout their 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, including those for self-medication, at the time they are dispensed.

Governments, universities and professional associations have a major responsibility to collaborate on improving undergraduate, postgraduate and continuing education in clinical pharmacology, therapeutics and drug information issues.

Appropriate drug information that is well presented is cost-effective in that it ensures that drugs are used properly and decreases inappropriate drug use; drug information activities should be financed from the national budget for the provision of drugs.

Drug information sheets

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

1. INN of each active substance.
2. Pharmacological data: a brief description of pharmacological properties 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).

The Committee also recognizes the need to develop appropriate drug information sheets for consumers.

15. 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 4.

16. Model List of Essential Drugs (eighth 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

[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.

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 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 antihypertensive 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 (*42*); (b) the Convention on Psychotropic Substances, 1971 (*43*); or (c) the Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (*44*).
(2) Specific expertise, diagnostic precision, individualization of dosage 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.
(10) Sustained-release preparations available. A proposal to include such a product in a national list of essential drugs should be justified by adequate documentation.

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 available in the WHO *model prescribing information* publications (*36, 38-40*), and in several other WHO publications (*45-47*). 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. It is necessary for individual countries to specify which drugs have priority in their country.

Drug	*Route of administration, dosage forms and strengths*[a]
1. Anaesthetics	
1.1 *General anaesthetics and oxygen*	
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 1:200 000 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 1:80 000
1.3 *Preoperative medication and sedation for short-term procedures*	
atropine	injection, 1 mg (sulfate) in 1-ml ampoule
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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
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 (sulfate or hydrochloride), 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)
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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
3. Antiallergics and drugs used in anaphylaxis *(continued)*	
epinephrine	injection, 1 mg (as hydrochloride or hydrogen tartrate) 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
□ DL-methionine	tablet, 250 mg
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 hexacyano ferrate(II) · $2H_2O$ (Prussian blue)	powder for oral administration
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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
5. Antiepileptics	
carbamazepine (10)	scored tablet, 100 mg, 200 mg
□ diazepam (1b)	injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)
ethosuximide	capsule, 250 mg
	syrup, 250 mg/5 ml
phenobarbital (1b)	tablet, 15–100 mg
	elixir, 15 mg/5 ml
phenytoin	capsule or tablet, 25 mg, 50 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	
albendazole	chewable tablet, 200 mg
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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.1 *Anthelminthics* (continued)	
6.1.2 Antifilarials	
diethylcarbamazine	tablet, 50 mg (dihydrogen citrate)
ivermectin	scored tablet, 6 mg
Complementary drug	
suramin sodium (B) (2, 7)	powder for injection, 1 g in vial
6.1.3 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	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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.2 *Antibacterials* (continued)	
6.2.1 Penicillins (continued)	
phenoxymethylpenicillin	tablet, 250 mg (as potassium salt)
	powder for oral suspension, 250 mg (as potassium salt)/5 ml
□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)/5 ml
	powder for injection, 1 g (as sodium succinate) in vial
doxycycline (5, 6)	capsule or tablet, 100 mg (as hyclate)
□ 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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.2 *Antibacterials* (continued)	
6.2.2 Other antibacterials (continued)	
□ 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)
Complementary drugs	
chloramphenicol (C)	oily suspension, 0.5 g (as sodium succinate)/ml in 2-ml ampoule
ciprofloxacin (B)	tablet, 250 mg (as hydrochloride)
clindamycin (B)	injection, 150 mg (as phosphate)/ml
nalidixic acid (B)	tablet, 250 mg, 500 mg
nitrofurantoin (B) (4, 7)	tablet, 100 mg
trimethoprim (B)	tablet, 100 mg, 200 mg

The need for and use of additional reserve antimicrobials for specific infections resistant to the antibacterials on the main list are discussed in section 6 of the text. Examples of reserve antimicrobials are cefalosporins and vancomycin.

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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.2 *Antibacterials* (continued)	
6.2.4 Antituberculosis drugs (continued)	
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 (7)	capsule or tablet, 125 mg, 250 mg
□ ketoconazole (2)	tablet, 200 mg
	oral suspension, 100 mg/5 ml
nystatin	tablet, 100 000, 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, 100 mg, 150 mg (as phosphate or sulfate)

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.4 *Antiprotozoal drugs* (continued)	
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, 100 mg, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
	injection, 40 mg (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoule
primaquine	tablet, 7.5 mg, 15 mg (as diphosphate)
□ 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] (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
mefloquine	tablet, 250 mg (as hydrochloride)
proguanil[c]	tablet, 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".

[b] For use only in combination with quinine.

[c] For use only in combination with chloroquine.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.4 *Antiprotozoal drugs* (continued)	
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
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, 1 mg (tartrate)
paracetamol	tablet, 300–500 mg
7.2 *For prophylaxis*	
□ propranolol	tablet, 20 mg, 40 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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
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*	
asparaginase (2)	powder for injection, 10 000 IU in vial
bleomycin (2)	powder for injection, 15 mg (as sulfate) in vial
calcium folinate (2)	tablet, 15 mg
	injection, 3 mg/ml in 10-ml ampoule
chlormethine (2)	powder for injection, 10 mg (hydrochloride) 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
□ 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
levamisole (2)	tablet, 50 mg (as hydrochloride)
mercaptopurine (2)	tablet, 50 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 organ transplantation.

□ Example of a therapeutic group.

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)	
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
8.3 *Hormones and antihormones*	
□ prednisolone	tablet, 5 mg
	powder for 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* (*48*) be considered essential. The drugs are included in the relevant sections of the model list, according to their therapeutic use, e.g. analgesics.	
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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
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
	nasal spray, 10 µg (acetate)/metered dose
heparin sodium	injection, 1000 IU/ml, 5000 IU/ml, 20 000 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)
11. Blood products and plasma substitutes	
11.1 *Plasma substitutes*	
□ dextran 70	injectable solution, 6%
□ polygeline	injectable solution, 3.5%

[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.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
11. Blood products and plasma substitutes *(continued)*	
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
□ propranolol	tablet, 10 mg, 40 mg (hydrochloride)
	injection, 1 mg (hydrochloride) in 1-ml ampoule
□ verapamil (10)	tablet, 40 mg, 80 mg (hydrochloride)
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, 10)	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 1992). *WHO Expert Committee on Biological Standardization. Forty-third report.* (WHO Technical Report Series, No. 840, 1994, Annex 2).

□ Example of a therapeutic group.

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
isoprenaline (C)	injection, 1 mg (hydrochloride)/ml
□ procainamide (B)	tablet, 250 mg, 500 mg (hydrochloride)
	injection, 100 mg (hydrochloride)/ml in 10-ml ampoule
□ quinidine (A) (7)	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 (10)	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

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
12. Cardiovascular drugs *(continued)*	
12.4 *Cardiac glycosides* (continued)	
Complementary drug	
digitoxin (B) (6)	tablet, 50 µg, 100 µg
	injection, 200 µg in 1-ml ampoule
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, 750 000 IU, in vial
13. Dermatological drugs (topical)	
13.1 *Antifungal drugs*	
benzoic acid + salicylic acid	ointment or cream, 6% + 3%
□ miconazole	ointment or cream, 2% (nitrate)
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%
□ 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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
13. Dermatological drugs (topical) *(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, 5%
dithranol	ointment, 0.1–2%
fluorouracil	ointment, 5%
□ podophyllum resin (7)	solution, 10–25%
salicylic acid	solution, 5%
13.6 *Scabicides and pediculicides*	
benzyl benzoate	lotion, 25%
permethrin	cream, 5%
	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)/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".

□ Example of a therapeutic group.

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)	solution, 5–8 g iodine in 100–250 ml
15. Disinfectants and antiseptics	
15.1 *Antiseptics*	
□ chlorhexidine	solution, 5% (digluconate) for dilution
hydrogen peroxide	solution, 3%
□ polyvidone iodine	solution, 10%
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.

□ Example of a therapeutic group.

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
17.6 *Cathartic drugs*	
□ senna	tablet, 7.5 mg (sennosides) (or traditional dosage forms)

[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".

□ Example of a therapeutic group.

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

17. Gastrointestinal drugs *(continued)*

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 only recommended when manufactured for immediate use.

□ Example of a therapeutic group.

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	
medroxyprogesterone acetate (B) (7, 8)	depot 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
18.6 *Ovulation inducers*	
□ clomifene (2, 8)	tablet, 50 mg (citrate)

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
18. Hormones, other endocrine drugs and contraceptives *(continued)*	
18.7 *Progestogens*	
norethisterone	tablet, 5 mg
Complementary drug	
medroxyprogesterone acetate (B)	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 serum	injection
diphtheria antitoxin	injection, 10 000 IU, 20 000 IU in vial
immunoglobulin, human normal (2)	injection (intramuscular)
immunoglobulin, human normal (2, 8)	injection (intravenous)
□ 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 1992). *WHO Expert Committee on Biological Standardization. Forty-third report.* WHO Technical Report Series, No. 840, 1994, Annex 2).

□ Example of a therapeutic group.

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
hepatitis B vaccine	injection
measles–mumps–rubella vaccine	injection
measles vaccine	injection
poliomyelitis vaccine (inactivated)	injection
poliomyelitis vaccine (live attenuated)	oral solution
tetanus 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, Mumps and Rubella Vaccines and Combined Vaccine (Live) (Revised 1992) (WHO Technical Report Series, No. 840, 1994); 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) and Amendment 1992 (WHO Technical Report Series, No. 840, 1994); Rabies Vaccine (Inactivated) for Human Use Produced in Continuous Cell Lines (Revised 1986) (WHO Technical Report Series, No. 760, 1987) and Amendment 1992 (WHO Technical Report Series, No. 840, 1994); Typhoid Vaccine (Live, Attenuated, Ty 21 a, Oral) (WHO Technical Report Series, No. 700, 1984); Vi Polysaccharide Typhoid Vaccine (WHO Technical Report Series, No. 840, 1994); Yellow Fever Vaccine (Revised 1975) (WHO Technical Report Series, No. 594, 1976) and Addendum 1987 (WHO Technical Report Series, No. 771, 1988).

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
19. Immunologicals *(continued)*	
19.3 *Vaccines*[b] (continued)	
19.3.2 For specific groups of individuals	
influenza vaccine	injection
meningococcal vaccine	injection
rabies vaccine	injection
rubella vaccine	injection
typhoid vaccine	injection
yellow fever vaccine	injection
20. Muscle relaxants (peripherally acting) and cholinesterase inhibitors	
□ alcuronium (2)	injection, 5 mg (chloride)/ml in 2-ml ampoule
□ neostigmine	tablet, 15 mg (bromide)
	injection, 500 µg, 2.5 mg (metilsulfate) in 1-ml ampoule
pyridostigmine (2, 8)	tablet, 60 mg (bromide)
	injection, 1 mg (bromide) in 1-ml ampoule
suxamethonium (2)	injection, 50 mg (chloride)/ml in 2-ml ampoule
	powder for injection (chloride)
Complementary drug	
vecuronium (C)	powder for injection, 10 mg (bromide) 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)

[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] See footnote on page 46.

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
21. Ophthalmological preparations *(continued)*	
21.2 *Anti-inflammatory agents*	
□ prednisolone	solution (eye drops), 0.5%
21.3 *Local anaesthetics*	
□ tetracaine	solution (eye drops), 0.5% (hydrochloride)
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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
24. Psychotherapeutic drugs	
24.1 *Drugs used in psychotic disorders*	
□ chlorpromazine	tablet, 100 mg (hydrochloride)
	syrup, 25 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
□ 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
24.2 *Drugs used in mood disorders*	
□ amitriptyline	tablet, 25 mg (hydrochloride)
lithium carbonate (2, 4)	capsule or tablet, 300 mg
24.3 *Drugs used for sedation and in generalized anxiety disorders*	
□ diazepam (1b)	scored tablet, 2 mg, 5 mg
24.4 *Drugs used in obsessive-compulsive disorders and panic attacks*	
clomipramine	capsule, 10 mg, 25 mg (hydrochloride)
25. Drugs acting on the respiratory tract	
25.1 *Antiasthmatic drugs*	
□ aminophylline (2, 10)	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 or hydrogen tartrate) 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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*[a]
25. Drugs acting on the respiratory tract *(continued)*	
25.1 *Antiasthmatic drugs* (continued)	
□ 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
Complementary drug	
□ cromoglicic acid (B)	inhalation (aerosol), 20 mg (sodium salt) per dose
25.2 *Antitussives*	
□ codeine (1a)	tablet, 10 mg (phosphate)
26. Solutions correcting water, electrolyte and acid-base disturbances	
26.1 *Oral*	
oral rehydration salts (for glucose–electrolyte solution)	for composition see 17.7.1 (p. 43)
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)

[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".

□ Example of a therapeutic group.

Drug	*Route of administration, dosage forms and strengths*
26. Solutions correcting water, electrolyte and acid-base disturbances* *(continued)*	
26.2 *Parenteral* (continued)	
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
26.3 *Miscellaneous*	
water for injection	2-ml, 5-ml, 10-ml ampoules
27. Vitamins and minerals*	
ascorbic acid	tablet, 50 mg
□ 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), 0.57 ml (308 mg iodine) in dispenser bottle
	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	in any appropriate formulation
thiamine	tablet, 50 mg (hydrochloride)
Complementary drug	
calcium gluconate (C) (2, 8)	injection, 100 mg/ml in 10-ml ampoule

* See footnotes on page 50.

17. 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*

Diazepam injection is deleted since it is not recommended for anaesthetic procedures of long duration.

1.3 *Preoperative medication and sedation for short-term procedures*

The name of this subsection is changed to indicate that diazepam may be used in short-term procedures.

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 8 (*28*) 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 rejected 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 urged 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

Chlorphenamine is listed as the prototype for the antihistamine H_1 antagonist class. This class includes drugs with less sedative action than the traditional antihistamines or with different therapeutic potencies. The selection of drugs in this class should be based on the intended therapeutic uses, the adverse reaction profile and the cost.

Section 5. Antiepileptics

The number (10) is added to carbamazepine since sustained-release preparations hold significant clinical advantage.

For phenytoin, a 50-mg tablet is added to improve dose titration.

Section 6. Anti-infective drugs

6.1.1 *Intestinal anthelminthics*

Albendazole is transferred to the main list since its use as a broad-spectrum anthelminthic is now well established. Tiabendazole is deleted from this section on account of its general toxicity.

6.1.2 *Antifilarials*

Suramin sodium is moved to the complementary list with the letter (B), since its use in onchocerciasis is limited to curative treatment of selected individuals.

6.2.1 *Penicillins*

Oral amoxicillin is preferred to oral ampicillin except in the treatment of shigellosis, for which the latter drug is still recommended.

The number (5) after benzathine benzylpenicillin is deleted since the Committee considers that it is open to misinterpretation.

6.2.2 *Other antibacterials*

Doxycycline is moved to the main list because it has a favourable pharmacokinetic profile and is the preferred tetracycline in many situations. The injectable formulation is deleted.

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.

Chloramphenicol oily suspension is added to the complementary list with the letter (C). It has been found to be helpful in catastrophic epidemics of meningococcal meningitis when the medical services are overwhelmed by the epidemic. For this reason, this product should be reserved for use in epidemics of meningococcal meningitis when the scale of the epidemic precludes any other form of antibiotic therapy.

Nalidixic acid is also added to the complementary list with the letter (B) for the treatment of resistant shigellosis.

Reserve antimicrobials: cefalosporins and vancomycin are mentioned.

6.2.4 *Antituberculosis drugs*

It is essential that all combination tablets 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 HIV than in those who are HIV-negative. Because of the high frequency of these adverse reactions, the combination tablets containing thioacetazone remain in 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*

The number (7) is added to griseofulvin in view of its adverse reaction profile.

6.4.1 *Antiamoebic and antigiardiasis drugs*

For chloroquine, a 100-mg tablet is added.

6.4.3 *Antimalarial drugs*

(a) For curative treatment

The square symbol preceding chloroquine is retained solely to accommodate hydroxychloroquine. A 100-mg tablet is added. Chloroquine injection, 40-mg base (as hydrochloride, phosphate or sulfate)/ml in 5-ml ampoules, is also added, since parenteral chloroquine is recommended for the treatment of severe and complicated falciparum malaria where the organism remains fully sensitive to chloroquine.

Tetracycline should be used only in combination with quinine.

(b) For prophylaxis

Mefloquine is transferred to the main list since it is increasingly being used in prophylaxis.

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.

Section 7. Antimigraine drugs

7.1 *For treatment of acute attack*

For ergotamine, the 2-mg tablet is replaced by a 1-mg tablet.

7.2 *For prophylaxis*

For propranolol, a 40-mg tablet has been added and the 10-mg tablet deleted.

Section 8. Antineoplastic and immunosuppressant drugs

8.2 *Cytotoxic drugs*

Asparaginase, chlormethine (mustine or mechlorethamine hydrochloride) and levamisole are added for the treatment of various cancers (see "Essential drugs for cancer chemotherapy", *49*).

Calcium folinate is moved from the complementary list and the footnote is deleted since this drug is used as adjunctive therapy in cancer of the colon.

8.3 *Hormones and antihormones*

Dexamethasone is deleted from this section since the Committee considers that the square symbol preceding prednisolone is sufficient.

Ethinylestradiol is deleted since it is not recommended as first-line treatment in prostate cancer.

Section 10. Drugs affecting the blood

10.2 *Drugs affecting coagulation*

A nasal formulation of desmopressin is added to the list since it is available in some countries.

Section 11. Blood products and plasma substitutes

11.2 *Plasma fractions for specific uses*

A square symbol is added to albumin to accommodate plasma and cryoprecipitate-poor plasma.

Section 12. Cardiovascular drugs

12.1 *Antianginal drugs*

Nifedipine capsules or tablets, 10 mg, are replaced by verapamil tablets, 40 mg and 80 mg, since the Committee considers this drug to be the calcium-channel blocker of choice. The number (10) is added because sustained-release preparations hold significant clinical advantage.

12.2 *Antidysrhythmic drugs*

The number (10) is added to verapamil because sustained-release preparations hold significant clinical advantage.

Isoprenaline injection, 1 mg/ml, is added as a complementary drug with the letter (C) for the emergency treatment of severe bradycardia.

The number (7) is added to quinidine in view of its adverse reaction profile.

12.3 *Antihypertensive drugs*

The number (10) is added to nifedipine because sustained-release preparations hold significant clinical advantage. Methyldopa in the complementary list refers to the L isomer only.

12.6 *Antithrombotic drugs*

For streptokinase, a strength of 750000 IU is added since the standard dose in myocardial infarction is 1.5 million IU.

Section 13. Dermatological drugs (topical)

13.1 *Antifungal drugs*

Nystatin is deleted as a topical agent because the other drugs listed are more effective.

13.2 *Anti-infective drugs*

Mupirocin is deleted because it is expensive and because the other drugs listed are adequate.

13.6 *Scabicides and pediculicides*

For permethrin, a 5% cream is added, since this is widely used in the treatment of scabies.

Section 15. Disinfectants and antiseptics

15.1 *Antiseptics*

Polyvidone iodine, 10% solution, now replaces iodine as the topical antiseptic agent of choice.

Section 16. Diuretics

The square symbol preceding mannitol is retained to indicate that sorbitol could serve as an alternative.

Section 17. Gastrointestinal drugs

17.4 *Anti-inflammatory drugs*

A square symbol is added to sulfasalazine to accommodate mesalazine, for the treatment of patients who are allergic to sulfonamides.

Section 18. Hormones, other endocrine drugs and contraceptives

18.6 *Ovulation inducers*

Clomifene is transferred to the main list since it is considered essential if a programme for the treatment of infertility is planned. It is not needed for any other purpose.

18.7 *Progestogens*

Medroxyprogesterone acetate is added to the complementary list as an alternative drug for hormone replacement therapy and for the treatment of dysfunctional uterine bleeding.

Section 19. Immunologicals

19.2 *Sera and immunoglobulins*

Intramuscular and intravenous preparations of immunoglobulin are listed separately since the indications for these two immunoglobulins are different. The numbers (2) and (8) are added to the intravenous preparation and the number (2) is added to the intramuscular preparation.

19.3.1 *For universal immunization*

Hepatitis B vaccine is transferred to the main list since it is now recommended by WHO as the seventh vaccine for childhood immunization.

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

Alcuronium chloride with a square symbol now replaces gallamine as the prototype muscle relaxant.

Pyridostigmine is transferred to the main list because of its importance in the treatment of myasthenia gravis.

Section 24. Psychotherapeutic drugs

This section is divided into four subsections as follows.

24.1 *Drugs used in psychotic disorders*

The square symbol preceding chlorpromazine is retained to accommodate any non-depot phenothiazine preparation and that preceding fluphenazine is retained to accommodate any neuroleptic depot preparation.

The square symbol preceding haloperidol is retained to indicate that any non-phenothiazine, non-depot preparation can be used in its place.

24.2 *Drugs used in mood disorders*

The square symbol preceding amitriptyline is retained to accommodate any tricyclic antidepressant.

24.3 *Drugs used for sedation and in generalized anxiety disorders*

The square symbol preceding diazepam is retained to indicate that any long-acting (half-life > 12 hours) benzodiazepine can be used in its place.

24.4 *Drugs used in obsessive–compulsive disorders and panic attacks*

Clomipramine is added to this new section in view of its usefulness in the treatment of panic attacks and obsessive–compulsive disorders.

Section 25. Drugs acting on the respiratory tract

The number (10) is added to aminophylline since sustained-release preparations hold significant clinical advantage.

The square symbol preceding beclometasone is added to accommodate other inhaled corticosteroids and that preceding epinephrine is added to accommodate the use of isoprenaline.

Ephedrine is deleted from the complementary list since it is no longer considered appropriate in the treatment of asthma.

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

26.1 *Oral*

For potassium chloride, the powder should be dissolved in water to make a 1 mmol/ml (74.5 mg/ml) solution for dispensing.

Section 27. Vitamins and minerals

Ascorbic acid is transferred to the main list.

An additional dosage form of iodized oil, 0.57 ml (308 mg iodine) in a dispenser bottle, is added because of its importance in the treatment of children.

Sodium fluoride in any appropriate formulation now replaces the specific dosage forms. The number (8) is deleted since these preparations are widely used in dental health care programmes and a square symbol is added to indicate that other formulations for dental prophylaxis are available.

18. 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.

19. Alphabetical list of essential drugs

Acknowledgement

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Annex 1

Provision and dissemination of drug information

Introduction

A WHO Consultation on the Provision and Dissemination of Drug Information met in Geneva from 7 to 11 December 1992. The meeting was opened on behalf of the Director-General by Dr J. F. Dunne, Director, Division of Drug Management and Policies, who explained that, because drug promotion is both product-specific and persuasive, and because it does not discuss the therapeutic options available to the prescriber, it needs to be complemented by independent, comparative prescribing information. This Consultation had been arranged to explore to what extent such information already exists, from both official and non-official sources in representative countries, and how it might be made more readily available to prescribers and consumers.

The discussions began with an overview of some of the drug information activities undertaken by WHO (see Appendix). The participants in the consultation noted that many developing countries depend upon WHO as a source of information about decisions taken by other drug regulatory authorities, although it is not always known how such information is used at national level. There was general agreement that, in many countries, there is scope for greater collaboration in generating drug information between governmental authorities, pharmaceutical companies and health professionals, particularly medical teachers in academic institutions.

The need for independent drug-related information

Rational prescribing is dependent upon the availability of clear, accurate, impartial, comparative information about medicines. This information needs to be available at all times to all health professionals responsible for prescribing, dispensing and administering medicines. Health professionals, in turn, have a responsibility to ensure that the patient or consumer is sufficiently informed to be able to use prescribed medicines to best advantage and without any unnecessary risks.[1]

The information given to health professionals should also indicate the prices of pharmaceutical products in order to provide a basis for cost-effective prescribing.

[1] At the CIOMS/WHO Consultation on the WHO Ethical Criteria for Medicinal Drug Promotion held in Geneva from 5 to 7 April 1993, it was established that patients had a right to know about the drugs they were being prescribed and that this requirement was an additional reason for providing reliable drug-related information.

Roles and responsibilities of interested parties

In many countries much of the available information about drugs is provided by pharmaceutical companies. Such companies also may support postgraduate education for doctors and pharmacists, and provide funding for the printing and publishing of educational material.

Since promotional material issued by pharmaceutical companies is both product-specific and persuasive, dependence on this material for prescribing purposes is unsatisfactory. It inevitably encourages the use of intensively promoted products in preference to cheaper and possibly more appropriate alternatives.

Seven groups were identified as having an interest in the provision of drug information: governments, the pharmaceutical industry, health professionals, educational institutions, patients, the public and the media. The participants in the consultation considered the roles and responsibilities of each of these groups in turn.

Governments

Governments should ensure that the needs for independent drug-related information are met. They should promote the establishment of a drug advisory committee to ensure collaboration between health professionals (doctors, pharmacists), universities, consumer groups and other nongovernmental agencies, as well as medical teachers in academic institutions, public health personnel and editors of independent drug bulletins. They should also:

- Assure the production of a national prescribers' formulary that contains therapeutic guidelines and is regularly updated and widely distributed.
- Provide other relevant information, including data on the approval of new drug products, drug usage, adverse drug effects and the findings of pharmacoepidemiological studies. In doing so, they should work, where appropriate, in collaboration with international health and development agencies, including WHO.
- Support and encourage the provision of impartial, comparative, clear and accurate information about medicines within independent drug bulletins and similar publications.
- Support the funding and distribution of independent drug bulletins where they do not already exist and assist in integrating the activities of everyone concerned with the provision of independent drug-related information.
- Ensure that such legislation as is necessary is enacted and implemented to control the quality of promotional activities undertaken by pharmaceutical companies.
- Support the establishment of independent drug information centres, which should be equipped: (i) to deal with requests from health care professionals for information about all aspects of drug use; and (ii) to gather and disseminate information about local patterns of drug use, drug misuse and abuse, and antimicrobial resistance.

Pharmaceutical companies

Pharmaceutical companies were recognized by the Consultation to have made a fundamental contribution to the welfare of patients and to possess a legitimate right to promote their products. The participants considered, however, that many sales techniques currently used are excessive and not in the best interests of patients. Bearing in mind the direct responsibility of pharmaceutical companies to the community, the participants recommended that such companies should:

- Adhere to legislation controlling the advertising and promotion of medicines, particularly that prohibiting the use of claims that are neither verifiable nor scientifically valid.
- Avoid using the media for disguised promotion of prescription drugs.
- Ensure that clinical trials are designed to produce information of direct relevance to the practice of medicine within the socioeconomic context of the countries in which they are performed, and that studies are undertaken to compare the efficacy of the new drug(s) with standard therapy.
- Provide prescribers and pharmacists, on request, with up-to-date and comprehensive information (that is not of commercial value) relating to the safety and efficacy of their products.

Health professionals

Health professionals, including doctors, pharmacists, nurses and their teachers, must have access to independent drug-related information, since they have direct contact with patients and prescribe the medicines that patients receive. They also determine the setting in which drugs are used, and they are able to assess clinical trial data to offer critical, impartial and independent advice on drug use. With these considerations in mind, the participants recommended that health professionals should:

- Make every attempt to keep abreast of information about the medicines they prescribe or supply.
- Assume the initiative to produce independent information (particularly formularies) on all aspects of drug use, both within their own professional organizations and in collaboration with others, taking into account the needs of their colleagues, their institutions, their patients and the public at large.

Medical schools and other training institutions

Medical schools and other training institutions should be recognized as having a valuable input to the development of government drug policy. They should improve undergraduate training in drug evaluation by upgrading relevant teaching programmes and making appropriate changes in the curriculum. They should also:

- Ensure that the undergraduate and postgraduate training programmes include topics such as the interpretation of clinical trials, risk/benefit

assessments, the rational use of drugs, the principles of essential (limited) drugs lists, the methods and impact of drug promotion, and the role of the media in influencing prescribing.
- Teach the principles of effective communication with patients.
- Ensure that the staffing complement of clinical departments includes personnel with a special interest in drug use.
- Improve training of clinical pharmacologists and clinical pharmacists.

Patients and the public

Patients and the public can themselves contribute to better use of medicines by becoming more active in the "therapeutic dialogue" with health care providers. The participants considered, in particular, that:

- Consumers' associations, patient groups, teachers, community leaders and professional associations – working either individually or in collaboration – should strive to inform patients and the public about the rational use of drugs.
- Drug information should be targeted at specific groups of users (such as pregnant women and children).
- Imaginative schemes should be developed to evoke the interest of the public using traditional cultural tools, including story-telling and "street theatre", as well as written materials and posters.

The media

The media, including radio, television and newspapers, have a strong influence on the perceptions and attitudes of the public. While the participants recognized that the media should be able to comment freely on matters of local and national interest, they considered, none the less, that there is a temptation to introduce an element of sensationalism into the reporting of medically related issues in a way that runs counter to the provision of rational health care. They therefore recommended that:

- Reporters should act responsibly, in accordance with prescribed codes of conduct, and with due regard to their influence on health care and the perceptions of patients.
- Reporters should check on the validity and significance of any drug-related story by seeking an informed independent opinion or consulting relevant professional associations before publishing or broadcasting reports.
- Informed health professionals should be encouraged to respond helpfully to requests for information from the media.
- Journalists should be wary of acting as spokespersons for promotional campaigns by the pharmaceutical industry.
- Health professionals and professional organizations should offer the media carefully researched and accurately presented material on health topics of public interest.

Preparation and publication of drug bulletins in developed and developing countries

The participants considered that there was a need for independent drug bulletins in countries at all stages of development. Such bulletins do not necessarily need to be issued at national level to be read and valued. Their value should be assessed, not in isolation, but as a contribution to the full range of materials – including, for example, a national formulary and an essential drugs list – through which accurate, verifiable, usable and impartial therapeutic advice is offered to health professionals. Bearing this in mind, the participants noted that:

- while the source of funding for drug bulletins varies from country to country, mechanisms should be in place everywhere to protect the intellectual independence of the editors;
- all funding agencies should respect this independence and not attempt to influence editorial direction;
- while the scope of drug bulletins is variable, all should aim to provide information of local relevance about any aspect of drug use (including traditional medicines and non-essential drugs) that is considered to be appropriate;
- whereas some bulletins produce original articles and reviews, others may provide abstracted versions of articles published elsewhere.

Dissemination of drug information to health professionals

All health professionals authorized to prescribe or administer drugs need access to a regularly updated national drug formulary, model drug information or locally prepared guidelines on priority health problems, and drug bulletins. To encourage full use of these information sources, the participants recommended that:

- Topics should be chosen that have relevance and appeal to the target readership, and the material should be presented in a style that is of immediate relevance to the practising clinician.
- Efforts should be made, through undergraduate and postgraduate training, posters, discussions, meetings and other means, to ensure that all potential users know that the information is available.

International exchange of drug-related information

Participants regarded the exchange of drug-related information between countries as essential and recommended that it should be assured through a variety of channels. The participants identified, in particular:

- intergovernmental communication between drug regulatory authorities and the clearinghouse function provided by WHO;
- the provision of reference material by organizations in developed countries to designated reference centres and key personnel in developing countries;
- the distribution of national drug formularies, drug bulletins and other drug-related materials through coordinating centres (such as WHO or the International Society of Drug Bulletins) to developing countries;

– the need, at international level, to organize training programmes for producers of drug information, and to provide grants to establish drug information centres.

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Appendix
Drug information available from WHO

The participants reviewed the drug information developed and disseminated by WHO in recent years.

Division of Drug Management and Policies

The Division of Drug Management and Policies is responsible for the provision of the following normative information on drugs.

1. WHO's Model List of Essential Drugs is revised and updated biennially by an Expert Committee on the basis of information provided from a wide variety of sources, including all technical units within the Organization, its expert advisory panels, nongovernmental organizations and the pharmaceutical industry.

2. Model prescribing information is being developed to provide source material for adaptation by national authorities, particularly in developing countries that wish to develop national drug formularies, drug compendia and similar material. Three volumes have been published to date, *Drugs used in anaesthesia* (*1*), *Drugs used in parasitic diseases* (*2*) and *Drugs used in mycobacterial diseases* (*3*), and a fourth, *Drugs used in sexually transmitted diseases and HIV infection* (*4*), is in press. Further volumes are in preparation, covering drugs used in skin diseases, neurology, gastrointestinal diseases, rheumatology and the management of chronic pain.

3. The WHO pharmaceuticals newsletter is issued monthly and provides a summary of the most recent data on the safety and efficacy of drugs moving in international commerce.

4. *WHO drug information* is a quarterly journal which provides an overview of topics relating to drug development and regulation that are of current relevance and importance. The objective is to bring issues that are of primary concern to drug regulatory authorities and pharmaceutical manufacturers to the attention of health professionals and policy-makers concerned with the rational use of drugs. It also includes the latest lists of proposed and recommended international nonproprietary names (INNs) for pharmaceutical substances.

5. The pharmaceutical section of the *United Nations' Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments* (*5*) provides details of specific restrictive regulatory actions taken by individual national drug regulatory authorities. It is regularly updated and is available to drug regulatory authorities, the pharmaceutical industry, and others concerned with the safe and rational use of drugs.

6. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce was introduced in 1975 (*6*) as a means of exchanging information between drug regulatory authorities in importing and exporting countries on the regulatory status of specific pharmaceutical products. The scheme was expanded in 1988 (*7*) to include drug substances as well as finished dosage forms, and provision was made for the exchange of all approved product information and labelling, as required by the product licence.

7. The WHO Programme on International Drug Monitoring, first established 25 years ago, continues to collect data on suspected adverse drug reactions. The database is now located within the WHO Collaborating Centre on International Drug Monitoring, Uppsala, Sweden, and contains several million reports of such reactions.

Action Programme on Essential Drugs

The Action Programme on Essential Drugs is the operational arm of WHO in the field of pharmaceuticals. Its mandate is to assist Member States in developing and implementing national drug policies. One key component of such policies is the development and dissemination of educational and informational materials for prescribers and patients, together with the development of legislation controlling the advertising and promotion of medicines. The Programme is currently providing technical and financial support to over 40 countries in the updating of pharmaceutical legislation; the preparation of national drug formularies; the preparation of therapeutic guidelines for different levels of the health care system, based on the drugs available at each level; the development of training courses for prescribers; and the adaptation of source materials by national authorities. Such country support also provides the opportunity to identify broad-based information needs and has led to the development, after national testing, of generic material such as the manual *Estimating drug requirements* (*8*), a draft model guide to good prescribing practice and a wide range of other technical materials with direct application. The Programme also produces a newsletter, the *Essential drugs monitor*, covering issues of drug policy, drug supply and use and related research, which is issued in English, French and Spanish and has a global readership of over 200 000.

The Programme also has a documentation centre, which provides reference materials on drugs free of charge to countries that, in most cases, would have no other access to such material. In 1992, the centre provided over 36 000 documents and publications worldwide. A bibliographic database is also available, both in print form and on diskette, which is consulted regularly by teachers and researchers, in addition to providing a technical resource for WHO personnel.

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Annex 2

Guidelines for antimicrobial susceptibility testing for intermediate-level laboratories in countries with limited resources

Introduction

Although many communicable diseases have been effectively contained, bacterial infections remain a major cause of morbidity and mortality, particularly in developing countries.

It has been stressed repeatedly by various WHO Expert Committees that the increasing prevalence of strains of common pathogenic bacteria resistant to widely available, relatively cheap antimicrobials, such as those included in WHO's Model List of Essential Drugs (*1*), is dangerously eroding their effectiveness, not only for the treatment of individual patients, but also for the community at large.

Whenever one such drug or class of drugs is used excessively, genetic changes favouring the emergence of antimicrobial-resistant bacteria tend to supervene. Although such changes can occur after only a single exposure in an individual patient, resistance usually emerges after a sustained period of use. Resistance is generally stable and passed on for several generations of bacteria. The spread of antimicrobial-resistant clones of bacteria within a host population or environment is also important, particularly in hospitals, where certain resistant organisms can become endemic and infect many patients. The problem is worsened by poor hygienic practices in hospitals and lack of adequate training in the control and containment of nosocomial and other infections. The spread of resistant bacteria within the community is of even greater importance. This seriously compromises empirical initial therapy of common bacterial infections and requires revision of routine antimicrobial strategies.

There is an urgent need for more systematic and coordinated international approaches to laboratory monitoring of antimicrobial susceptibility. Microbiological laboratories, including national reference laboratories, need to be established in developing as well as developed countries if the resistance of important bacterial pathogens is to be monitored. In response to this need, the WHONET program was developed by the WHO Collaborating Center for Surveillance of Antimicrobial Resistance (*2, 3*).[1] The program is designed both to manage susceptibility data for any medical centre and to link such centres into a surveillance network. It is now operating in some 100 hospitals, mostly in the United States, and is expanding in South America and the

[1] Available on request from the WHO Collaborating Center for Surveillance of Antimicrobial Resistance, Microbiology, Brigham and Women's Hospital, Boston, MA 02115, USA.

western Pacific region. The program will not be fully effective, however, until every country has a national reference laboratory that is actively reporting to this network.

The concept of reserve antimicrobials was introduced to WHO's Model List of Essential Drugs in 1989 (*4*), as a result of increasing concern about the emergence of important pathogens that were shown to have developed resistance to all normally appropriate essential antimicrobials. A reserve antimicrobial was defined as an antimicrobial which "may be useful in a wide range of infections, but in order to reduce the risk of development of resistance and because of its relatively high cost, it would be inappropriate to recommend its unrestricted use". This concept is of practical relevance, however, only when adequate laboratory facilities are available for obtaining accurate data on the prevailing antimicrobial susceptibility patterns of important bacterial pathogens. Without these facilities, the health of seriously ill patients could be endangered.

If antimicrobial resistance is to be controlled, several measures need to be undertaken:

1. Routine surveillance of antimicrobial-resistant bacteria using standardized, predictive test methods should be introduced in hospital and community settings.
2. Antimicrobial prescribing guidelines should be developed that will ensure effective treatment and not promote the emergence and spread of antimicrobial-resistant bacteria.
3. Comprehensive national programmes that conform to standards of good laboratory practice should be implemented, with the objective of assuring the quality and availability of antimicrobials.
4. Adequate training of technical personnel should be ensured.
5. Systems should be developed within the context of the WHONET program, whereby each country can collate and disseminate information on antimicrobial resistance to hospitals and health workers.

The following guidelines concern routine surveillance of antimicrobial-resistant bacteria using tests that can be undertaken in intermediate-level laboratories.

Susceptibility testing

Since the majority of bacterial infections that occur in humans are not investigated by microbiological methods, antimicrobial treatment is usually initiated on the basis of a presumptive etiological diagnosis determined by the clinical history and physical findings. Microbiological investigations are carried out in cases where the etiology is uncertain, in severe infections when patients fail to respond to empirical therapy or develop a new infection during the course of therapy, or for public health

purposes. Additionally, *in vitro* susceptibility tests are performed when an organism is known to have unpredictable susceptibility.

For routine monitoring, susceptibility tests are carried out using antimicrobials to which the organism is normally susceptible in order to determine whether resistance has emerged. Depending on the prevalence of resistance, recommendations for antimicrobial therapy may need to be modified.

Clinically and epidemiologically important bacteria and essential antimicrobials for susceptibility testing

General principles

1. The antimicrobial substances listed in these guidelines are commonly used in treatment protocols. This list is illustrative rather than comprehensive; other drugs may be important in various countries or regions.
2. Some of the drugs listed are index compounds representative of a defined group of drugs, e.g. oxacillin resistance in staphylococci indicates resistance to other β-lactam antimicrobials.
3. Provided that satisfactory laboratory methods are employed, it is relatively easy to detect resistance in rapidly growing bacteria. In contrast, detection of resistance in bacteria with complex nutritional requirements (fastidious bacteria) and anaerobic bacteria requires a high degree of technical expertise. In such circumstances, testing should be carried out in central reference laboratories, wherever possible.

Community-acquired infections

These infections are caused by organisms highly prevalent in the community. Some can be treated on an outpatient basis, while others will be severe enough to require admission of the patient to hospital for diagnosis and therapy.

Causative organisms (Community-acquired infections)	Drugs used as potential markers of antimicrobial resistance[a]
Staphylococcus aureus	benzylpenicillin erythromycin gentamicin oxacillin
Streptococcus pneumoniae	benzylpenicillin resistance, as predicted by the oxacillin disc test chloramphenicol erythromycin sulfamethoxazole + trimethoprim

Causative organisms (Community-acquired infections)	Drugs used as potential markers of antimicrobial resistance[a]
Streptococcus pyogenes	(benzylpenicillin) erythromycin
Haemophilus influenzae	ampicillin chloramphenicol sulfamethoxazole + trimethoprim
Neisseria gonorrhoeae	benzylpenicillin (ceftriaxone)[b] (ciprofloxacin)[b] tetracycline
Escherichia coli (urinary tract infection)	ampicillin (cefalosporin)[c] (fluoroquinolone) (gentamicin) nalidixic acid nitrofurantoin sulfamethoxazole + trimethoprim sulfonamide
Salmonella typhi and other invasive *Salmonella* spp.	ampicillin (cefotaxime) chloramphenicol (fluoroquinolone) sulfamethoxazole + trimethoprim
Shigella spp.	ampicillin (chloramphenicol) (fluoroquinolone) nalidixic acid[d] sulfamethoxazole + trimethoprim tetracycline
Vibrio cholerae	(chloramphenicol) (erythromycin) nitrofurantoin sulfamethoxazole + trimethoprim tetracycline

Hospital-acquired infections

These infections arise in patients who either are in hospital or have recently been discharged from hospital (usually within the past month). The causative organism is derived either from the patient's endogenous bacterial flora or from the flora endemic in the hospital.

Causative organisms (Hospital-acquired infections)	Drugs used as potential markers of antimicrobial resistance[a]
Staphylococcus aureus	benzylpenicillin erythromycin gentamicin oxacillin (vancomycin)
Coagulase-negative staphylococci	benzylpenicillin erythromycin gentamicin oxacillin (vancomycin)
Enterococci	ampicillin gentamicin[e] (vancomycin)
Pathogenic Gram-negative bacilli epidemic or endemic in hospitals, including *Enterobacter* spp., *Escherichia coli, Klebsiella* spp. and *Salmonella* spp.	ampicillin (cefalosporin)[c] chloramphenicol (fluoroquinolone) gentamicin sulfamethoxazole + trimethoprim
Pseudomonas aeruginosa	(ceftazidime) (fluoroquinolone) gentamicin piperacillin

Notes to tables

[a] Where the antimicrobial is given in parentheses, results need to be reported to the clinician only when resistance is found to one or more of the other antimicrobials listed in the same group.

[b] Reserve antimicrobial recommended for single-dose therapy of uncomplicated *Neisseria gonorrhoeae* infections where there is a high prevalence of resistance to first-line essential antimicrobials.

[c] A first-generation cefalosporin should be used such as cefalotin (representing the group cefalotin, cefalexin and cefadroxil) or cefazolin (representing the group cefazolin and cefaclor). Use of a broad-spectrum cefalosporin such as ceftazidime may be considered to ensure recognition of an extended spectrum of β-lactamase-mediated resistance.

[d] Reserve antimicrobial recommended for the treatment of shigellosis.

[e] Should be used to detect high-level resistance (minimum inhibitory concentration or MIC >500 mg/l) only.

Laboratory facilities required

In most developing countries, health laboratory services are generally organized at three levels:

1. Peripheral laboratories, including those attached to health centres and first referral hospitals (district hospitals).
2. Intermediate-level laboratories, situated in regional or provincial hospitals.
3. Central reference laboratories, usually located in the capital city or in a university hospital.

Facilities for bacteriological culture and antimicrobial susceptibility testing are generally not available at the peripheral level. Laboratory support in microbiology will be limited to microscopy and to some simple and rapid tests for the detection of antibodies (typhoid, syphilis) or antigens (meningitis, chlamydial infections).

Most intermediate-level laboratories should have the facilities to culture, identify and establish the antimicrobial susceptibility of common pathogens such as *Staphylococcus* spp., *Streptococcus pneumoniae, S. pyogenes,* enterococci, *Haemophilus influenzae, Neisseria gonorrhoeae, N. meningitidis, Salmonella* spp., *Shigella* spp., *Vibrio cholerae* and nosocomial Gram-negative bacilli. Susceptibility testing should be performed, at least for rapidly growing pathogens, when it is considered clinically necessary. For fastidious bacteria, testing may be limited to rapid, inexpensive methods, notably testing of *H. influenzae* and *N. gonorrhoeae* for β-lactamase production and screening of *S. pneumoniae* using 1-μg oxacillin discs as a marker for penicillin resistance.

All isolates of *Shigella, Salmonella* and *Vibrio* spp. and representative isolates of *Streptococcus pneumoniae, H. influenzae, N. meningitidis* and *N. gonorrhoeae* should be forwarded to a central reference laboratory, in an appropriate transport medium with refrigeration, for confirmation of identity, typing and epidemiological studies. A proportion of the isolates should be tested for antimicrobial susceptibility (for quality assurance purposes).

Laboratory requirements at the intermediate level

A special room should be available for bacteriological procedures, including antimicrobial susceptibility testing. It should include a simple safety cabinet for handling cultures of dangerous pathogens (e.g. *Salmonella typhi*), and facilities for safe disposal of specimens and cultures.

The standard equipment should include:

- an autoclave;
- an incubator with a thermostat regulated at 35 °C;
- Bunsen burners or incineration lamps;

- a refrigerator with a freezer-compartment suitable for correct storage of antimicrobial discs, prepared media and certain heat-labile reagents. Opened discs will retain potency for one month at 4–8 °C, while unopened disc stocks should be deep-frozen at –20 °C until used.

In addition to the standard routine culture media needed for isolation and identification of bacteria, the following media and materials are required for disc diffusion testing using the Kirby-Bauer method (see Appendix 1):

- Mueller-Hinton agar from a reputable manufacturer;
- antimicrobial discs of the recommended potency;
- barium sulfate standard for preparation of the standardized inoculum;
- sterile swabs for application of the inoculum;
- a ruler or calipers for measuring the diameter of the inhibition zones;
- standard bacterial strains for internal quality control.

The following are also needed for testing fastidious organisms:

- a candle jar;
- blood and appropriate growth supplements for preparation of Mueller-Hinton chocolate agar (for testing *Haemophilus influenzae*);
- haemoglobin and appropriate growth supplements for preparation of gonococcal chocolate (GC) agar (for testing *N. gonorrhoeae*);
- blood agar (5% blood in Mueller-Hinton agar) for testing *Streptococcus pneumoniae;*
- appropriate discs or reagents for determining β-lactamase production.

Recommended testing method

Strict adherence to well established techniques (Appendix 1) and regular quality control of media and reagents are necessary if reproducible and reliable results are to be assured. Any unusual or unexpected susceptibility test results should be confirmed by a central reference laboratory.

The laboratory must be able to identify bacteria correctly and consistently (Appendix 2) before undertaking susceptibility testing. This applies to common Gram-positive and Gram-negative bacteria, as well as to more technically demanding species.

Disc diffusion tests, which are both economical and simple to use (5), are widely employed for testing individual isolates of pathogens. However, standardized procedures must be carefully followed if test results from different laboratories are to be comparable. The modified Kirby-Bauer disc diffusion method has been carefully monitored by the United States National Committee for Clinical Laboratory Standards (NCCLS) and is satisfactory, provided it is rigorously standardized. Several other methods have been described (5), which also involve the use of controlled media, standard disc concentrations and strict compliance with agreed guidelines.

Pathogens to be tested

Most non-fastidious rapidly growing aerobic bacteria can grow on Mueller-Hinton agar or other recommended agars for susceptibility testing. For these organisms, susceptibility testing using antimicrobial discs is the most practical method. Other pathogens that could be considered for testing include the Enterobacteriaceae, *Pseudomonas* spp., *Enterococcus* spp., *Neisseria meningitidis* for penicillin resistance, and *Streptococcus pyogenes* for erythromycin resistance. The choice of other organisms for susceptibility testing will be influenced by local factors. In serious invasive infections such as pneumococcal septicaemia, an oxacillin disc test is used for detecting penicillin resistance, and in *H. influenzae* meningitis, a test for β-lactamase production is carried out. These tests may avert the need to use expensive broad-spectrum antimicrobials.

Susceptibility testing of the following organisms should be undertaken on the basis of their importance to the individual patient or to the region.

Staphylococcus aureus and coagulase-negative staphylococci

All isolates from wounds or exudates should be identified and tested. Routine testing using oxacillin as the index drug should be performed by a disc diffusion test (see Appendix 1) on Mueller-Hinton agar. This requires:

- incubation at 35 °C for a full 24 hours;
- careful examination for colonies growing within the inhibition zone;
- confirmation of meticillin (oxacillin) resistance using Mueller-Hinton agar supplemented with 4% sodium chloride and 6 mg/l of oxacillin.

Streptococcus pneumoniae

All strains isolated from blood and cerebrospinal fluid and a proportion of those from the respiratory tract should be identified and tested. Penicillin resistance may be moderate (MIC 0.12–1 mg/l) or high (MIC >1 mg/l), and can be detected using a 1-μg oxacillin disc for screening. Penicillin resistance should be confirmed quantitatively in a central reference laboratory.

Haemophilus influenzae

All strains isolated from cerebrospinal fluid or blood and a proportion of respiratory isolates should be tested. Special media are required. At intermediate-level laboratories, tests for β-lactamase production can be performed to predict ampicillin resistance using nitrocefin discs, a starch-iodine procedure or an acidimetric method. Resistance to chloramphenicol and sulfamethoxazole + trimethoprim is best detected by disc diffusion tests, preferably in a central reference laboratory.

Neisseria gonorrhoeae
A sample of isolates should be tested annually, preferably in a central reference laboratory. Testing should be conducted using defined enrichment media incubated in 3-5% carbon dioxide. β-Lactamase production can be detected using nitrocefin discs, a starch-iodine procedure or an acidimetric method. Non-enzymic resistance to penicillin, tetracycline, ceftriaxone and fluoroquinolone can be detected by the standardized disc diffusion method.

Enterococcus spp.
Both *E. faecalis* and *E. faecium* (the most prevalent species) can be identified to genus level by testing on bile-aesculin agar. Both show some natural low-level resistance to aminoglycosides and a higher level of resistance to several other antimicrobials. Discs containing at least 120 µg of gentamicin are required to detect strains exhibiting high-level resistance to gentamicin (MIC >500 mg/l). Standard discs are available from several sources; however, it should be noted that the criteria for interpretation vary with the supplier.

Salmonella typhi
All isolates should be identified and tested for antimicrobial susceptibility.

Salmonella spp. (other than S. typhi)
All isolates from specimens other than faeces should be identified and tested. In addition, the antimicrobial susceptibility of faecal isolates should be monitored periodically.

Shigella spp.
Except in epidemic situations in which the causative organism has been confirmed, all isolates should be identified and tested for antimicrobial susceptibility.

Mycobacterium tuberculosis
Testing should be performed in a central reference laboratory with technical expertise in the identification and culture of mycobacteria.

Guidelines for scoring antimicrobial susceptibility

There is no formal international agreement, as yet, on scoring for antimicrobial susceptibility. However, many countries, including France, Germany, Japan, Sweden, the United Kingdom and the USA, have developed national standards based on standardized methods. *These standards demand the precise adoption of a specific method, including adherence to the prescribed medium, the antimicrobial content of the disc and the density of the inoculum. Accordingly, guidelines for interpreting the results cannot be transcribed from one methodology to another.*

At present, NCCLS methodologies, standards and guidelines (*7*) are the most extensively used. These guidelines are regularly updated (Appendices 1 and 3) and provide a suitable framework for implementation for countries where national standardized methods are not in use. The interpretive criteria (NCCLS) for the essential drugs indicated for monitoring patterns of antimicrobial resistance are provided in Appendix 4.

Quality assurance

Each laboratory performing antimicrobial susceptibility tests should have an internal procedure for quality control. The laboratory should use standard reference strains that are tested in parallel with the clinical cultures, preferably on a weekly basis. The selection of the standard strains for quality control will depend upon the organisms and antimicrobials tested, e.g. *S. aureus* ATCC 25923 should be selected when testing Gram-positive clinical isolates and *E. coli* ATCC 25922 should be selected when testing non-fastidious Gram-negative bacilli. The test results should be carefully recorded and possible causes for values outside prescribed limits should be investigated.

Some countries now additionally require laboratories to submit to external proficiency tests involving the identification of potential pathogens as well as an assessment of the accuracy of antimicrobial susceptibility tests as a means of inter-laboratory comparison. All laboratories are encouraged to participate in such programmes.

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7. National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial disc susceptibility tests. Approved standard,* 5th ed. Villanova, PA, NCCLS, 1992; 1993 (NCCLS document no. M2-A5; M100-S4).

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Appendix 1

Summary protocol for antimicrobial susceptibility testing by the disc diffusion method[1]

The technique described below refers to the Kirby-Bauer method, which is widely available and has been well documented. If other disc diffusion methods are employed, it should be ensured that the appropriate media, antimicrobial discs and interpretive guidelines are used.

Reagents

Mueller-Hinton agar

1. Prepare the Mueller-Hinton agar medium from a quality control-tested lot according to the manufacturer's recommendations.
2. Pour the medium into the plates. Allow to set on a level surface. A 9-cm plate requires approximately 25–30 ml of medium, while a 14-cm plate requires about 60–70 ml.
3. Store the plates at 2–8 °C, pH 7.2–7.4.

Antimicrobial discs

Any commercially available discs with the appropriate diameter and stated amount of antimicrobial can be used. The discs should be stored at –20 °C. During the test, the discs should be kept at 4 °C and allowed to reach room temperature before being opened, to minimize the amount of condensation that occurs when warm air reaches the cold container.

Turbidity standard

Use McFarland 0.5 turbidity standard (barium sulfate), prepared from barium chloride dihydrate and sulfuric acid (for details, see reference *1*). The standard should be stored in the dark and dispensed in 4–6-ml tubes. Shake immediately before use.

Procedure

1. To prepare the inoculum from the primary culture, touch with a loop the tops of each of 4 or 5 well isolated colonies, of similar appearance, of the organism to be tested. Transfer this growth to a tube of saline or clear broth.
2. Compare the tube with the turbidity standard and adjust the density of the test suspension to that of the standard by adding more bacteria or more sterile saline or clear broth. Proper adjustment of the turbidity of

[1] A more detailed description of this protocol is available in the WHO publication *Basic laboratory procedures in clinical bacteriology* (*1*).

the inoculum is essential to ensure that the resulting lawn of growth is confluent or almost confluent.

3. Inoculate the plates by dipping a sterile cotton swab into the inoculum. Remove excess inoculum by pressing and rotating the swab firmly against the side of the tube above the level of the liquid.
4. Streak the swab evenly over the surface of the medium (in three directions). Leave the inoculum to dry for a few minutes at room temperature with the lid closed.
5. Using a pair of sterile forceps, place the antimicrobial discs at least 24 mm apart on the inoculated plates. A maximum of 6 discs (2 for fastidious species) can be used on a 9-cm plate. If a 14-cm plate is used, up to 11 discs can be used (5 for fastidious species).
6. Place the plates in an incubator at 35 °C. The period of incubation depends on the organism to be tested, as follows:
   - staphylococci – 24 hours;
   - *Haemophilus influenzae* and *Neisseria* spp. – 20-24 hours in 3-5% carbon dioxide or in a candle jar;
   - all other species – 16-18 hours.
7. Measure the diameter of each zone of inhibition (including the diameter of the disc) to the nearest mm. Interpret the results according to the critical diameters shown in Appendix 4.
8. Record the results for the test and control plates.

Reference

1. Antimicrobial susceptibility testing. In: Vandepitte J et al., eds. *Basic laboratory procedures in clinical bacteriology.* Geneva, World Health Organization, 1991: 78-95.

Appendix 2

Minimum features for identification of clinical pathogens

The principal pathogens requiring accurate identification for the purpose of antimicrobial sensitivity testing are listed below. The minimum characteristics and tests for identification are also listed. These conform to those listed in the WHO publication *Basic laboratory procedures in clinical bacteriology* and other widely recognized references.

Organism	Minimum features for identification
Staphylococcus aureus	Gram-positive cocci in clusters Catalase-positive Coagulase-positive
Staphylococci (coagulase-negative)	Gram-positive cocci in clusters Catalase-positive Coagulase-negative
Streptococcus pneumoniae	Gram-positive, oval-shaped cocci in pairs or short chains Green (α-)haemolytic colonies Catalase-negative Zone of inhibition around optochin disc Soluble in bile
Streptococcus pyogenes (group A)	Gram-positive cocci in chains β-Haemolytic colonies Catalase-negative Susceptible to bacitracin (disc potency 0.04 µg) Resistant to sulfamethoxazole + trimethoprim (disc potency 23.75 µg + 1.25 µg)
Enterococci	Gram-positive cocci in pairs or short chains Catalase-negative Hydrolysis in bile-aesculin agar Growth in 6.5% sodium chloride broth
Haemophilus influenzae	Gram-negative, slender coccobacilli Non-haemolytic satellite colonies around colonies of staphylococci on blood-agar plates (X and V factor requirement) No growth on blood-free media

Organism	Minimum features for identification
Neisseria gonorrhoeae	Gram-negative, oval-shaped diplococci with concave opposing edges and long axes parallel Oxidase-positive Growth on selective GC media No growth on nutrient agar Maltose not fermented (Negative for γ-glutamyl aminopeptidase)
Neisseria meningitidis	Gram-negative, oval-shaped diplococci with concave opposing edges and long axes parallel Oxidase-positive Growth on selective GC media No growth on nutrient agar Maltose fermented (Positive for γ-glutamyl aminopeptidase)
Escherichia coli	Gram-negative, motile bacilli Indole-positive Gas produced on acid triple sugar iron (TSI) agar slant (no hydrogen sulfide produced) (Positive for β-glucuronidase on 4-nitrophenyl-β-D-glucopyranosiduronic acid (PGUA))
Klebsiella spp.	Gram-negative, non-motile bacilli Indole-negative (except *K. oxytoca*) Lysine-positive on lysine-iron agar (LIA) slant Gas produced on acid TSI agar slant (no hydrogen sulfide produced)
Salmonella spp.	Gram-negative, motile bacilli Gas produced on acid, alkaline or neutral TSI agar slant (except *S. typhi*) Lysine-positive on LIA slant (except "*S. paratyphi*-A") Hydrogen sulfide produced on TSI and LIA slants (except some strains of "*S. paratyphi*-A")
Shigella spp.	Gram-negative, non-motile bacilli Lysine-negative Oxidase-negative No gas produced on acid, alkaline or neutral TSI agar slant (except some strains in a few serotypes), no hydrogen sulfide produced

Appendix 3
Zone diameter limits for control strains[a]

The values given in the table below refer to the Kirby-Bauer technique and do not apply to other disc diffusion methods.

Antimicrobial agent	Disc content	Diameter of zone of inhibition (mm)				
		E. coli (ATCC 25922)	*S. aureus* (ATCC 25923)	*H. influenzae* (ATCC 49247)	*N. gonorrhoeae* (ATCC 49226)	*P. aeruginosa* (ATCC 27853)
ampicillin	10 µg	16-22	27-35	14-22	–	–
benzylpenicillin	10 IU	–	26-37	–	26-34	–
cefalotin	30 µg	17-22	29-37	–	–	–
cefazolin	30 µg	23-29	29-35	–	–	–
cefotaxime	30 µg	29-35	25-31	27-35	34-38	18-22
ceftazidime	30 µg	25-32	16-20	25-33	–	22-29
ceftriaxone	30 µg	29-35	22-28	28-36	39-51	17-23
chloramphenicol	30 µg	21-27	19-26	28-36	–	–
ciprofloxacin	5 µg	30-40	22-30	29-37	48-58	25-33
erythromycin	15 µg	–	22-30	–	–	–

[a] Reproduced, with minor modifications, from National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial disc susceptibility tests. Approved standard.* Villanova, PA, NCCLS, 1992; 1993 (NCCLS document no. M2-A5; **13** (24)). Permission to use portions of M2-A5 has been granted by NCCLS. The above zone diameter limits for control strains are valid only if the methodology in M2-A5 is followed. NCCLS frequently updates these limits; the current M2 standard may be obtained from NCCLS, 771 E. Lancaster Avenue, Villanova, PA 19085, USA.

Antimicrobial agent	Disc content	Diameter of zone of inhibition (mm)				
		E. coli (ATCC 25922)	*S. aureus* (ATCC 25923)	*H. influenzae* (ATCC 49247)	*N. gonorrhoeae* (ATCC 49226)	*P. aeruginosa* (ATCC 27853)
gentamicin	10 µg	19-26	19-27	–	–	16-21
nalidixic acid	30 µg	22-28	–	–	–	–
nitrofurantoin	300 µg	20-25	18-22	–	–	–
oxacillin	1 µg	–	18-24	–	–	–
piperacillin	100 µg	24-30	–	–	–	25-33
sulfonamide	300 µg	18-26	24-34	–	–	–
tetracycline	30 µg	18-25	19-28	–	30-42	–
trimethoprim	5 µg	21-28	19-26	–	–	–
trimethoprim + sulfamethoxazole	1.25 µg + 23.75 µg	24-32	24-32	23-31	–	–
vancomycin	30 µg	–	15-19	–	–	–

Notes

1. Quality control tests should be performed at least weekly if organisms are processed on a daily basis. However, if testing is infrequent and/or irregularly performed, control strains should be processed concurrently with the clinical isolates.
2. Zone diameter limits for *E. coli, S. aureus* and *P. aeruginosa* are derived from tests on Mueller-Hinton agar.
3. Zone diameter limits for *Haemophilus* and gonococci are derived from tests on *Haemophilus* test medium (HTM) and supplemented GC agar, respectively.

Appendix 4
Interpretative chart of zone sizes[a, b]

The values given in the table below refer to the Kirby-Bauer technique and should not be used to interpret results obtained using other disc diffusion methods.

Antimicrobial agent	Disc potency	Diameter of zone of inhibition (mm)		
		Susceptible	Intermediate	Resistant
β-Lactams				
ampicillin when testing:				
enterococci	10 µg	⩾ 17	–	⩽ 16
Gram-negative organisms	10 µg	⩾ 17	14-16	⩽ 13
Haemophilus spp.	10 µg	⩾ 22	19-21	⩽ 18
benzylpenicillin when testing:				
N. gonorrhoeae[c, d]	10 IU	⩾ 47	27-46	⩽ 26
staphylococci	10 IU	⩾ 29	–	⩽ 28
streptococci	10 IU	⩾ 28	20-27	⩽ 19
cefalotin[e]	30 µg	⩾ 18	15-17	⩽ 14
cefazolin[e]	30 µg	⩾ 18	15-17	⩽ 14
cefotaxime[e]	30 µg	⩾ 23	15-22	⩽ 14
ceftazidime[e]	30 µg	⩾ 18	15-17	⩽ 14
ceftriaxone[e] when testing *N. gonorrhoeae*[f, g]	30 µg	⩾ 35	–	–
oxacillin[h] when testing:				
Streptococcus pneumoniae for penicillin susceptibility[f]	1 µg	⩾ 20	–	⩽ 19
staphylococci	1 µg	⩾ 13	11-12	⩽ 10
piperacillin when testing *P. aeruginosa*	100 µg	⩾ 18	–	⩽ 17

Antimicrobial agent	Disc potency	Diameter of zone of inhibition (mm)		
		Susceptible	Intermediate	Resistant
Quinolones				
ciprofloxacin when testing:				
Gram-negative enteric bacilli	5 µg	≥ 21	16-20	≤ 15
N. gonorrhoeae[f,g]	5 µg	≥ 36	–	–
nalidixic acid	30 µg	≥ 19	14-18	≤ 13
Other drugs				
chloramphenicol when testing:				
Gram-negative enteric bacilli	30 µg	≥ 18	13-17	≤ 12
Haemophilus spp. and *S. pneumoniae*[f,i]	30 µg	≥ 26	–	≤ 25
erythromycin	15 µg	≥ 23	14-22	≤ 13
gentamicin[j]	10 µg	≥ 15	13-14	≤ 12
nitrofurantoin[k]	300 µg	≥ 17	15-16	≤ 14
sulfonamides	300 µg	≥ 17	13-16	≤ 12
tetracycline when testing:				
Gram-negative enteric bacilli	30 µg	≥ 19	15-18	≤ 14
N. gonorrhoeae[c,d]	30 µg	≥ 38	31-37	≤ 30
trimethoprim	5 µg	≥ 16	11-15	≤ 10
trimethoprim + sulfamethoxazole[l]	1.25 µg + 23.75 µg	≥ 16	11-15	≤ 10
vancomycin when testing:				
enterococci	30 µg	≥ 17	15-16	≤ 14
other Gram-positive organisms[f]	30 µg	≥ 12	10-11	≤ 9

[a] Reproduced, with minor modifications, from National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial disc susceptibility tests. Approved standard.* 5th ed. Villanova, PA, NCCLS, 1992; 1993 (NCCLS document no. M2-A5; **13** (24)). Permission to use portions of M2-A5 has been granted by NCCLS. The interpretive data are valid only if the methodology in M2-A5 is followed. NCCLS frequently updates these data; the current M2 standard may be obtained from NCCLS, 771 E. Lancaster Avenue, Villanova, PA 19085, USA.

[b] The three categories of antimicrobial sensitivity are as follows:
- Susceptible: the infection caused by the tested strain is likely to respond to treatment with this drug, at the recommended dosage.
- Resistant: the infection caused by the tested strain is expected not to respond to treatment with this drug.
- Intermediate: the organism's response to therapy is unpredictable.

[c] An intermediate category for *N. gonorrhoeae* indicates a lower cure rate (85–95%) among infected patients compared to more than 95% cure rates for susceptible strains.

[d] Gonococci with 10 IU penicillin disc zones of ⩽19 mm are likely to be β-lactamase producers. With tetracycline 30-µg discs, zone diameters of ⩽19 mm usually indicate a plasmid-mediated tetracycline-resistant *N. gonorrhoeae* (TRNG) strain (MIC correlate ⩾16 mg/l).

[e] Choices for cefalosporin surveillance testing: cefalotin represents the group cefalotin, cefalexin and cefadroxil, while cefazolin represents cefazolin and cefaclor. Ceftazidime maximizes recognition of extended spectrum β-lactamase-mediated resistance; cefotaxime is used for testing against salmonellae; and ceftriaxone is a reserve antimicrobial used for gonococcal testing only.

[f] Strains yielding zone diameter results suggestive of a non-susceptible category should be submitted to a central reference laboratory for further testing.

[g] For these drugs, the current rarity of well documented resistant strains precludes the definition of any category other than susceptible.

[h] Oxacillin (representing the group oxacillin, meticillin, nafcillin, cloxacillin, dicloxacillin and flucloxacillin) is used in testing because of its greater resistance to deterioration during storage and its application to antimicrobial susceptibility testing of *S. pneumoniae.* Oxacillin resistance among staphylococci implies resistance to all β-lactams (penicillins, cefalosporins, carbapenems and β-lactamase inhibitor combinations).

[i] The criteria utilized by the NCCLS have been modified for use in laboratories in developing countries, e.g. no intermediate category.

[j] Testing for high-level aminoglycoside resistance should be performed by the agar dilution method (brain-heart infusion or BHI medium) with a screening concentration of 500 mg of gentamicin per litre. Alternatively, antimicrobial discs containing high levels of gentamicin (⩾120 µg) may be available for this purpose in some areas.

[k] Used to predict susceptibility to furazolidone.

[l] Also known as co-trimoxazole.

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Annex 3
Guidelines for good clinical practice (GCP) for trials on pharmaceutical products[1]

[1] This text was developed in consultation with national drug regulatory authorities within WHO's Member States. It was also discussed during two informal consultations convened by the Division of Drug Management and Policies, WHO, Geneva, from 26 to 27 June 1991 and 29 June to 3 July 1992. The participants were: Ms M. Cone, International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Geneva, Switzerland; Professor P. Dayer, International Union of Pharmacology (IUPHAR), Brussels, Belgium; Professor I. Darmansjah, University of Jakarta, Jakarta, Indonesia; Dr J.F. Dunne, Director, Division of Drug Management and Policies, WHO, Geneva, Switzerland *(Joint Secretary)*; Dr Y. Hirayama, New Drugs Division, Ministry of Health and Welfare, Tokyo, Japan; Professor E. Hvidberg, University Hospital, Copenhagen, Denmark *(Chairman)*; Dr J. Idänpään-Heikkilä, Associate Director, Division of Drug Management and Policies, WHO, Geneva, Switzerland *(Joint Secretary)*; Mr R. Laderman, Center for Drug Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA; Professor V.H. Lepakhin, Russian State Center for Drug Expertise, Moscow, Russian Federation; Dr P. Maurice, Ciba-Geigy, Basel, Switzerland; Professor J.O.M. Pobee, School of Medicine, Lusaka, Zambia; Mr M. Tsukano, New Drugs Division, Ministry of Health and Welfare, Tokyo, Japan; Dr S. Westman-Naeser, Medical Products Agency, Uppsala, Sweden; Professor A. Zanini, Institute of Biomedical Science, São Paulo, Brazil; Professor Zhu Jun-Ren, Shanghai Medical University, Shanghai, China.

Introduction

The purpose of these Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products is to set globally applicable standards for the conduct of such biomedical research on human subjects. They are based on provisions already promulgated in a number of countries, including Australia, Canada, European Community countries, Japan, Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) and the United States. These provisions inevitably vary somewhat in content and emphasis, but all are consonant with regard to the prerequisites to be satisfied and the principles to be applied as a basis for assuring the ethical and scientific integrity of clinical trials. Indeed, they have provided a formal basis for mutual recognition of clinical data generated within the respective countries. Every care has been taken, in developing the present Guidelines as a practicable administrative tool for use by WHO's Member States, to assure their compatibility with existing national and other provisions. It is hoped, on the basis of further consultations, to seek formal acceptance of the Guidelines by Member States as a contribution to harmonization of national standards and to facilitating the movement of pharmaceutical products internationally. No question arises, however, of challenging or replacing existing national regulations or requirements. The objective is to provide a complementary standard that can be applied worldwide. In countries where national regulations or requirements do not exist or require supplementation, relevant government officials may designate or adopt, in part or in whole, these Guidelines as the basis on which clinical trials will be conducted.

The Guidelines are addressed not only to investigators, but also to ethics review committees, pharmaceutical manufacturers and other sponsors of research, and drug regulatory authorities. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, these Guidelines not only serve the interests of the parties actively involved in the research process, but protect the rights and safety of subjects, including patients, and ensure that the investigations are directed to the advancement of public health objectives.

The Guidelines are intended specifically to be applied during all stages of drug development both prior to and subsequent to product registration and marketing, but they are also applicable, in whole or in part, to biomedical research in general. They should also provide a resource for editors to determine the acceptability of reported research for publication and, specifically, of any study that could influence the use or the terms of registration of a pharmaceutical product. Not least, they provide an educational tool that should become familiar to everyone engaged in biomedical research and, in particular, to every newly trained doctor.

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

adverse event
Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.

adverse reaction
A response to a pharmaceutical product that is noxious and unintended and that occurs at doses normally used or tested in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. In clinical trials, injuries caused by overdosing, abuse or dependence and interactions with any other product should be considered adverse reactions.

audit of a trial
A systematic examination, carried out independently of those directly involved in the clinical trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the case-report forms (CRFs) are consonant with those found in hospital files and other original records.

case-report form (CRF)
A document that is used to record data on each trial subject during the course of the clinical trial, as defined by the protocol. The data should be collected by procedures that guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

clinical trial
A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, is given below:

Phase I
These are the first trials of a new active ingredient or new formulation in humans, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of the safety, and the pharmacokinetic and, where possible, pharmacodynamic profile of the active ingredient in humans.

Phase II
These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

Phase III
Trials in larger (and possibly varied) patient groups, with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

Phase IV
Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration, new combinations, etc. are normally considered as trials on new pharmaceutical products.

comparator product
A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

confidentiality
Maintenance of the privacy of trial subjects, including their personal identity and all personal medical information.

contract
A document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation or distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed.

contract research organization (CRO)
A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

escape treatment
Any supplementary treatment provided to relieve a trial subject of symptoms caused by the investigated disease in the clinical trial. Escape treatment is often used in order to alleviate pain in placebo-controlled trials.

ethics committee
An independent body (a review board or an institutional, regional or national committee), constituted of medical professionals and non-medical members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects participating in a particular clinical trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

final report
A comprehensive description of the clinical trial after its completion, including a description of experimental methods (including statistical methods) and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethical, statistical and clinical appraisal.

Good Clinical Practice (GCP)
A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

Good Manufacturing Practice (GMP)
That part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. In these guidelines, GMP refers to the current GMP guidelines published by WHO (*1*).

informed consent
A subject's voluntary confirmation of willingness to participate in a particular clinical trial, and the documentation thereof. This consent should only be sought after all appropriate information has been given about the trial, including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative

treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki (see Appendix 1).

inspection
An officially conducted examination (i.e. review of the conduct of the clinical trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of the trial and/or the site of the sponsor in order to verify adherence to Good Clinical Practice as set out in these guidelines.

investigator
A person responsible for the clinical trial and for the rights, health and welfare of the subjects participating in the trial. The investigator should have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials. Decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry.

investigational labelling
Labelling developed specifically for products involved in a clinical trial.

investigational product (synonym: study product)
Any pharmaceutical product or placebo being tested or used as a reference in a clinical trial.

investigator's brochure
A collection of data for the investigator consisting of all available relevant information on the investigational product(s), including chemical and pharmaceutical data, toxicological, pharmacokinetic and pharmacodynamic data obtained from studies in animals as well as in humans, and the results of earlier clinical trials. There should be adequate data to justify the nature, scale and duration of the proposed trial and to evaluate the potential safety and need for special precautions. If new data are generated, the investigator's brochure must be updated.

monitor
A person appointed by, and responsible to, the sponsor or contract research organization (CRO) for monitoring and reporting on the progress of the clinical trial and for verification of data.

patient/subject file
A collection of data consisting of all relevant information on the patient or subject (such as a hospital file, consultation record or special subject file) that permits the authenticity of the information presented in the case-report form to be verified and, where necessary, completed or corrected. The conditions regulating the use and consultation of such documents must be respected.

pharmaceutical product
Any substance or combination of substances that has a therapeutic, prophylactic or diagnostic use, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

principal investigator
The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicentre trials.

protocol
A document that states the background, rationale and objectives of the clinical trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also serve as a contract.

quality assurance relating to clinical trials
Systems and quality control procedures that are established to ensure that the trial is performed and the data are generated in compliance with Good Clinical Practice. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOP), reporting procedures, and professional or personnel qualifications.

raw data
All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies in the form of photocopies, microfiches, etc. Raw data can also include photographic negatives, microfilm or magnetic media (e.g. computer diskettes).

serious adverse event
An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

sponsor
An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

standard operating procedures (SOP)
Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient

implementation and performance of all the functions and activities for a particular trial as described in this document.

study product (synonym: investigational product)
Any pharmaceutical product or placebo being tested or used as a reference in a clinical trial.

trial subject
An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control. The individual may be:

- a healthy person who volunteers to participate in a trial;
- a person with a condition unrelated to the use of the investigational product;
- a person (usually a patient) whose condition is relevant to the use of the investigational product.

validation
The action of proving, in accordance with the principles of Good Clinical Practice, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually leads to the expected results.

verification (validation) of data
The procedures carried out to ensure that the data contained in the final report match the original observations. These procedures may apply to raw data, data in case-report forms (in hard copy or electronic form), computer printouts and statistical analyses and tables.

witness
A person who will not be influenced in any way by those who are involved in the clinical trial, who is present and may provide assistance if required when the subject's informed consent is obtained, and documents that this consent is given freely by signing and dating the informed-consent form.

1. Provisions and prerequisites for a clinical trial

1.1 *Justification for the trial*

It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of a particular clinical trial be thoroughly considered and that the chosen options be scientifically sound and ethically justified.

1.2 *Ethical principles*

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of

the Declaration of Helsinki (see Appendix 1). Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) or non-maleficence (doing no harm), as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects[1] or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles (see sections 3 and 4).

1.3 *Supporting data for the investigational product*

Pre-clinical studies that provide sufficient documentation of the potential safety of a pharmaceutical product for the intended investigational use are a prerequisite for a clinical trial. Information about manufacturing procedures and data from tests performed on the actual product should establish that it is of suitable quality for the intended investigational use. The pharmaceutical, pre-clinical and clinical data should be appropriate to the phase of the trial, and the amount of supporting data should be appropriate to the size and duration of the proposed trial. In addition, a compilation of information on the safety and efficacy of the investigational product obtained in previous and ongoing clinical trials is required for planning and conducting subsequent trials.

1.4 *Investigator and site(s) of investigation*

Each investigator should have appropriate expertise, qualifications and competence to undertake the proposed study. Prior to the clinical trial, the investigator(s) and the sponsor should establish an agreement on the protocol, standard operating procedures (SOP), the monitoring and auditing of the trial, and the allocation of trial-related responsibilities. The trial site should be adequate to enable the trial to be conducted safely and efficiently (see section 4.7).

1.5 *Regulatory requirements*

Countries in which clinical trials are performed should have regulations governing the way in which these studies can be conducted. The pre-trial agreement between the sponsor and investigator(s) should designate the parties responsible for meeting each applicable regulatory requirement (e.g. application to or notification of the trial to the relevant authority, amendments to the trial protocol, reporting of adverse events and reactions, and notifications to the ethics committee). All parties involved

[1] These guidelines are updated regularly by the Council for International Organizations of Medical Sciences (CIOMS); the most recent update was published in 1993 (*2*).

in a clinical trial should comply fully with the existing national regulations or requirements. In countries where regulations do not exist or require supplementation, relevant government officials may designate, in part or in whole, these Guidelines as the basis on which clinical trials will be conducted. The use of these Guidelines should not prevent their eventual adaptation into national regulations or laws. Neither should they be used to supersede an existing national requirement in countries where the national requirement is more rigorous.

2. The protocol

The clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator and the sponsor. Any change(s) subsequently required must be similarly agreed on and signed by the investigator and sponsor and appended to the protocol as amendments.

The protocol, appendices and any other relevant documentation should state the aim of the trial and the procedures to be used; the reasons for proposing that the trial should be undertaken on humans; the nature and degree of any known risks; the groups from which it is proposed that trial subjects be selected; and the means for ensuring that they are adequately informed before they give their consent. Other important items to be included in a clinical trial protocol are listed in Appendix 2.

The protocol, appendices and other relevant documentation should be reviewed from a scientific and ethical standpoint by one or more (if required by local laws and regulations) review bodies (e.g. institutional review board, peer review committee, ethics committee or drug regulatory authority), constituted appropriately for this purpose and independent of the investigator(s) and sponsor.

3. Protection of trial subjects

The personal integrity and welfare of the trial subject as defined in the Declaration of Helsinki should be the primary concern of all parties involved in the conduct of a clinical trial and the review of the protocol, but it is the ultimate responsibility of the investigator, who must also take into consideration the scientific validity of the trial.

3.1 *Declaration of Helsinki*

The current revision of the Declaration of Helsinki (Appendix 1) is the accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials. Any departures from the Declaration must be justified and stated in the protocol. Independent assurance that subjects are protected can be provided only by an ethics committee and freely obtained informed consent.

3.2 *Ethics committee*

The role of the ethics committee (or other board responsible for reviewing the trial) is to ensure the protection of the rights and welfare of human subjects participating in clinical trials, as defined by the current revision of the Declaration of Helsinki and national and other relevant regulations, and to provide public reassurance, *inter alia,* by previewing trial protocols, etc. (see section 2).

The ethics committee should be constituted and operated so that its tasks can be executed free from bias and from any influence of those who are conducting the trial.

The ethics committee should have documented policies and procedures as a basis for its work, which should be available to the public. These should set out the authority under which the committee is established, the number of members elected and their qualifications, a definition of what it will review, and its authority to intervene and maintain records of its activities. The documents should also state how frequently the committee will meet and how it will interact with the investigator and/or sponsor.

The investigator, or the investigator and the sponsor, must consult the relevant ethics committee(s) regarding the suitability of a proposed clinical trial protocol (including appendices and amendments) and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects.

The ethics committee has an ongoing responsibility for the ethical conduct of research, and therefore must be informed of all subsequent amendments to the protocol and of any serious adverse events occurring during the trial, or other new information likely to affect the safety of the subjects or the conduct of the trial. The ethics committee should be consulted if a re-evaluation of the ethical aspects of the trial appears to be required, or if there is any doubt regarding the importance of a protocol change or new information.

Subjects must not be entered into the clinical trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures. The ethics committee should give its opinion and advice in writing within a reasonable time, clearly identifying the trial protocol, itemizing the documents studied and stating the date of review. A list of those present at the committee meeting, including their professional status, should be attached.

When reviewing a clinical trial proposal, the ethics committee should consider the following:

(a) The acceptability of the investigator for the proposed trial, on the basis of sufficient information made available to the committee, in terms of his or her qualifications, experience, availability for the duration of the trial, supporting staff and available facilities.

(b) The suitability of the protocol, including the objectives of the study and the justification of predictable risks and inconveniences weighed against the anticipated benefits for the subjects and/or others, and the efficiency of its design, i.e. the potential for reaching sound conclusions with the smallest possible exposure of subjects.

(c) The means by which trial subjects will be recruited, necessary or appropriate information will be given, and consent will be obtained. This is particularly important in the case of trials involving subjects who are members of a group with a hierarchical structure or another vulnerable group (see section 3.3, (e)-(f)).

(d) The adequacy and completeness of the information, which should be written in a language and at a level of complexity understandable to everyone involved, to be given to the subjects, their relatives, guardians or, if necessary, legal representatives. All such written information must be submitted in its final form to the ethics committee.

(e) Provision, if any, for compensation or treatment in the case of death or other loss or injury of a subject, if attributable to a clinical trial, and details of any insurance or indemnity (a source of legal and financial support) to cover the liability of the investigator(s) and sponsor (see section 5.9).

(f) The appropriateness of the extent and form of payment through which the sponsor will remunerate or compensate the organization(s) and/or investigator(s) conducting the trial and the trial subjects, as required by local laws and regulations.

(g) The acceptability of any proposed amendments to the protocol that are likely to affect the safety of the subjects or the conduct of the trial.

3.3 *Informed consent*

The principles of informed consent in the current revisions of the Declaration of Helsinki (Appendix 1) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2) should be implemented in each clinical trial.

(a) Information should be given in a language and at a level of complexity understandable to the subject in both oral and written form whenever possible. No subject should be obliged to participate in the trial. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to enquire about details of the trial. The information must make clear that the trial is a research procedure, that participation is voluntary, and that refusal to participate or withdrawal from the trial at any stage will not prejudice the subject's care, rights and welfare. Subjects must be allowed sufficient time, determined by their health condition and/or the illness, to enquire about details of the trial and to decide whether or not they wish to participate.

(b) The subject must be made aware and consent that personal information may be scrutinized during the monitoring, auditing or inspection of the trial by authorized persons, the sponsor or relevant authorities, and that participation and personal information in the trial will be treated as confidential and will not be publicly available. This principle may be modified by national laws and regulations.

(c) The subject must have access to information about insurance, if any, and other procedures for compensation and treatment should he or she be injured or disabled by participating in the trial.

(d) If a subject consents to participate after a full and comprehensive explanation of the study, this consent should be appropriately recorded. The explanation should include the aim of the study; the expected benefits for the subjects and/or others; the possibility of allocation to a reference treatment or placebo; the risks and inconveniences – e.g. invasive procedures; and, where appropriate, an explanation of alternative, recognized medical therapy. Consent must be documented either by the subject's dated signature or in agreement with local laws and regulations by the signature of an independent witness who records the subject's consent. In either case, the subject must be informed that signature confirms only that consent is based on the information provided, and that the subject has freely chosen to participate without prejudice to legal and ethical rights, while reserving the right to withdraw from the study at his or her own initiative at any time, without having to give any reason. If, however, the reason for withdrawal relates to an adverse event(s), the investigator should be informed.

(e) Careful consideration should be given to ensuring the freedom of consent obtained from members of a group with a hierarchical structure – such as medical, pharmacy and nursing students, hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. In such cases the willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of the hierarchy in case of refusal to participate. Other vulnerable groups whose consent also needs special consideration include patients with incurable diseases, people in nursing homes, prisoners or detainees, the unemployed or people on a very low income, patients in emergency departments, some ethnic and racial minority groups, the homeless, nomads and refugees. If such categories are part of the population to be enrolled in a clinical trial, the ethics committee should consider carefully the appropriateness of the informed-consent process.

(f) If the subject is incapable of giving personal consent (e.g. in the case of children or adults who are unconscious or suffering from severe mental illness or disability), the inclusion of such subjects in a trial may be acceptable, provided: it is permitted by local laws and regulations; the ethics committee is, in principle, in agreement; and

the investigator thinks that participation will promote the welfare and be in the interest of the subject. The agreement of a legally acceptable representative that participation will promote the welfare and be in the interest of the subject should also be recorded by a dated signature. If the patient is incapable of giving either signed informed consent or witnessed signed verbal consent, this fact must be documented by the investigator, stating the reasons.

(g) In a non-therapeutic study, i.e. when there is no direct clinical benefit to the subject, consent must always be given by the subject and documented by his or her dated signature.

(h) The trial subjects should be informed that they have access to appropriate (identified) persons to obtain further information and medical advice or escape treatment, if necessary.

(i) Any information that becomes available during the trial which may be of relevance to the trial subjects must be made known to them by the investigator.

(j) The subjects should be informed of the circumstances under which the investigator or sponsor might terminate their participation in the study.

3.4 *Confidentiality*

The investigator must establish secure safeguards of confidentiality of research data as described in the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2) (see also section 3.3).

4. Responsibilities of the investigator

4.1 *Medical care of trial subjects*

The investigator is responsible for providing adequate and safe medical care (or dental care, where appropriate) of subjects during the clinical trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made.

4.2 *Qualifications*

The investigator should:

- have qualifications and competence in accordance with local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials (decisions relating to, and the provision of, medical or dental care must always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry);

- have good knowledge and experience of the field of medicine or dentistry defined by the protocol;
- be experienced in clinical trial research methods or receive scientific support from an experienced colleague;
- be aware of available relevant data and literature and all information provided by the sponsor;
- have access to human and other resources to assume full responsibility for the proper conduct of the trial;
- be aware of and comply with national regulatory and legal and ethical requirements.

4.3 *Selection of trial subjects*

The investigator is responsible for ensuring the unbiased selection of an adequate number of suitable subjects as defined by the protocol. It may be necessary to secure the cooperation of other physicians in order to obtain a sufficient number of subjects.

In order to assess the probability of recruiting an adequate number of subjects for the study, it may be useful to determine prospectively or to review retrospectively (e.g. on the basis of the clinic's records) the availability of potential subjects. The investigator should check whether subjects so identified can or could be included according to the protocol.

The patient's own physician should, when relevant and with the patient's consent, be informed of the patient's participation in the clinical trial.

4.4 *Compliance with the protocol*

The investigator must agree with and sign the protocol (or another legally acceptable document mentioning the agreement with the protocol) with the sponsor, and confirm in writing that he or she has read, understands and will work according to the protocol and Good Clinical Practice.

The investigator is responsible for ensuring that the protocol is strictly followed. The investigator should not make any changes in the study without the agreement of the sponsor, except when necessary to eliminate an apparent immediate hazard or danger to a trial subject. Any change should be in the form of a protocol amendment, appended to the original protocol and signed by the investigator and the sponsor. Amendments which are likely to affect the safety of a subject or the conduct of the clinical trial should be submitted in writing to the ethics committee (see section 3.2) and drug regulatory authority and implemented only after approval has been received.

The investigator should take any steps judged necessary to protect the safety of the trial subject, whether specified in the protocol or not. Any such steps must be documented.

4.5 *Information for subjects and informed consent*

The investigator is responsible for giving adequate information to subjects about the clinical trial. The current version of the Declaration of Helsinki (Appendix 1) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (*2*) should be followed. The nature of the investigational pharmaceutical product, its stage of development and the complexity of the study should be considered in determining the nature and extent of the information that should be provided.

Information should be given in both oral and written form in a language understandable to the subject. The protocol should state when and by whom such information will be provided, and how the provision of information should be recorded.

Informed consent must be obtained according to the principles described in section 3.3.

The investigator should also supply subjects with, and encourage them to carry with them, information about their participation in the trial and information about the person(s) to contact in case of emergency.

4.6 *The investigational product*

The investigator must be thoroughly familiar with the properties, effects and safety of the investigational pharmaceutical product(s), including pre-trial data, as described in the investigator's brochure or in the literature. The investigator should be aware of all relevant new data on the product that appears during the course of the clinical trial.

4.7 *The trial site*

Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the investigational product and the potential risks involved. The trial site must have adequate facilities, including laboratories, equipment and sufficient medical, paramedical and clerical staff to support the trial and to deal with all reasonably foreseeable emergencies. All laboratory assays must be validated, and principles of Good Laboratory Practice (GLP) should be observed.

The investigator should ensure that he or she has sufficient time to conduct and complete the trial, and that other commitments or trials do not divert essential subjects, resources or facilities away from the trial in hand.

The investigator must provide adequate information to all staff involved in the trial.

The investigator must notify or obtain approval for the trial from the relevant local hospital (medical, administrative) management in compliance with existing regulations.

4.8 *Notification of the trial or submission to the drug regulatory authority*

As governed by national regulations, the investigator, sponsor, or investigator jointly with the sponsor should give notification of the clinical trial to, or obtain approval from, the drug regulatory authority. Any submission to the drug regulatory authority should be in writing and dated, and contain sufficient information to identify the protocol.

4.9 *Review by an ethics committee*

Prior to its commencement, the investigator must ensure that the proposed clinical trial has been reviewed and accepted in writing by the relevant independent ethics committee(s) (see section 3.2). Any submission to and acceptance by the ethics committee should be in writing and dated, and contain sufficient information to identify the protocol or other submitted documents.

4.10 *Serious adverse events or reactions*

The investigator must take appropriate measures to ensure the safety of clinical trial subjects (see also section 7). The investigator is also responsible for notifying (with documentation) the relevant health authorities, the sponsor and, when applicable, the ethics committee immediately in the case of serious adverse events or reactions, as governed by national regulations.

4.11 *Financing*

The relationship between the investigator and the sponsor in matters such as financial support, fees and honorarium payments in kind must be stated in writing in the protocol or contract. The protocol or contract should be available to the drug regulatory authority and ethics committee on demand.

4.12 *Monitoring, auditing and inspection*

The investigator must be prepared to receive and be available for periodic visits by the monitor(s) and accept the implications of such visits (see also section 6). In addition, the investigator must accept auditing and/or inspection by the relevant health authorities and by persons appointed by the sponsor for quality assurance.

4.13 *Record-keeping and handling of data*

See section 8.

4.14 *Handling of and accountability for pharmaceutical products for trial*

See section 10.

4.15 *Termination of the trial*

In the case of premature termination of the clinical trial, the investigator must inform the drug regulatory authority, the ethics committee and, where applicable, the sponsor. Reasons for termination must be stated in writing.

4.16 *Final report*

After completion of the clinical trial, a final report must be drawn up and submitted to the drug regulatory authority. The report should be dated and signed by the investigator in accordance with local regulations to verify responsibility for the validity of the data.

4.17 *Trials in which the investigator is the sponsor*

In clinical trials in which the investigator is the sponsor, he or she is responsible for the corresponding functions (see section 5).

5. Responsibilities of the sponsor

The sponsor is often a pharmaceutical company, but may also be an individual, the investigator, or an independent institution or organization that initiates, funds, organizes and oversees the conduct of a clinical trial. When the sponsor is a foreign company or organization, it should have a local representative to fulfil the appropriate local responsibilities as governed by national regulations.

The sponsor is responsible for providing the investigational and comparator (if any) products, as well as appropriate information to support the safe use of those products. In addition, the sponsor is responsible for ensuring that the trial is conducted in accordance with sound scientific principles and Good Clinical Practice standards by selecting qualified investigators, providing a protocol and ensuring protocol compliance, establishing the distribution of trial-related responsibilities, and providing facilities, equipment and staff for management of the trial, record-keeping, handling of data, monitoring, and quality assurance. The sponsor is also ultimately responsible for ensuring compliance with applicable legal, ethical and regulatory requirements (although local regulations may designate certain required activities as responsibilities of the investigator), and for providing compensation or indemnity in the event of trial-related injury or death, according to local laws and regulations.

5.1 *Selection of the investigator(s)*

The sponsor is responsible for selecting the investigator(s), taking into account the appropriateness and availability of the proposed trial site and facilities, and being assured of the investigator's qualifications and availability to conduct the study.

5.2 *Delegation of responsibilities*

The sponsor is responsible for agreeing with the investigator(s) on the allocation of protocol-related responsibilities, including data processing, breaking of the trial code, handling of statistics, preparation of trial reports, and preparation and submission of documentation to the ethics committee, the drug regulatory authority and any other required review bodies. This agreement should be confirmed in writing (protocol, contract or alternative document) prior to the trial.

The sponsor may transfer any or all clinical trial-related activities to a scientific body (commercial, academic or other), or to a contract research organization (CRO). Any such transfer should be documented in writing.

5.3 *Compliance with the protocol and procedures*

The sponsor is responsible for assuring the investigator's agreement to undertake the clinical trial as described in the protocol, and according to Good Clinical Practice, and to accept procedures for data recording (particularly in the case-report form or CRF), monitoring, audits and inspections. The sponsor and the investigator must sign the protocol or an alternative document confirming this agreement.

Both the sponsor and the investigator should agree to any amendment to the protocol before it is implemented and this should be documented in writing.

Amendments which may affect the safety of the subjects or the conduct of the trial should be submitted in writing to the ethics committee (see section 3.2) through the investigator or, if applicable, directly by the sponsor. The sponsor should provide justification for the amendments. If required, the amendments should be submitted to the drug regulatory authority. The amendments should not be implemented until all the required approvals have been obtained, unless the delay caused by this process is likely to expose the subjects to an immediate hazard or danger.

5.4 *Product information*

As a prerequisite to planning the clinical trial, the sponsor is responsible for providing the investigator with available chemical/pharmaceutical, toxicological, pharmacological and clinical data (including data from previous and ongoing trials) regarding the investigational product and, where appropriate, the comparator product(s). This information should be accurate and adequate to justify the nature, scale and duration of the trial. In addition, the sponsor must bring any relevant new information arising during the trial to the attention of the investigator.

The sponsor is responsible for preparing and providing to investigators an investigator's brochure, which must include all relevant information about the product(s) and must be supplemented and/or updated whenever any relevant new information is available.

5.5 *Safety information*

The sponsor must inform the investigator(s) promptly of any relevant information on safety that becomes available during the clinical trial and ensure that the ethics committee and the drug regulatory authority are notified by the investigator(s), if required (see section 7).

5.6 *Investigational product*

The sponsor is responsible for supplying the investigational pharmaceutical product(s) and, if applicable, comparator products, prepared in accordance with the principles of Good Manufacturing Practice (GMP) (see also section 10). The product(s) should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration and safeguard blinding procedures (if applicable); appropriate investigational labelling should be affixed.

Sufficient samples of each batch and a record of analyses and characteristics must be kept for reference so that, if necessary, an independent laboratory is able to re-check the investigational product(s), e.g. for quality control or bioequivalence.

Records of the quantities of investigational pharmaceutical products supplied must be maintained with batch or serial numbers. The sponsor must ensure that the investigator is able to establish a system within his or her institution for the adequate and safe handling, storage, use, return (to the investigator or sponsor) and, if appropriate, destruction of the investigational product(s).

5.7 *Trial management and handling of data*

The sponsor should appoint appropriate individuals and/or committees for managing and supervising the clinical trial, handling and verifying the data obtained, statistical processing, and preparing the trial report (see section 8).

5.8 *Standard operating procedures*

Where warranted by the number or scale of clinical trials conducted, it is recommended that the sponsor establish written standard operating procedures (SOP) to comply with Good Clinical Practice.

5.9 *Compensation for subjects and investigators*

As required by national law or regulations, the sponsor should provide adequate compensation or treatment for subjects in the event of trial-related injury or death, and provide indemnity for the investigator, except in the case of claims resulting from malpractice and/or negligence (see section 3.2, (e)-(f)).

5.10 *Monitoring*

The sponsor must appoint suitable and appropriately trained monitors and clinical research support personnel, and provide ongoing training to ensure that they are suitably qualified and to keep them up to date with new developments.

5.11 *Quality assurance*

The sponsor should establish a system or systems of quality assurance (including independent auditing) to ensure that the conduct of the clinical trial and the generation, documentation and reporting of data comply with the protocol, Good Clinical Practice standards and applicable regulatory requirements. The system should operate independently of those involved in conducting or monitoring the trial (see section 12).

5.12 *Study reports*

The sponsor is responsible for ensuring the preparation and appropriate approval(s) of a comprehensive final clinical study report suitable for regulatory purposes, whether or not the trial has been completed. The sponsor must also submit any relevant safety information (including safety updates) that becomes available during the trial and/or annual reports as required by the relevant health authorities.

5.13 *Handling of adverse events*

The sponsor should provide special forms for reporting any adverse events that occur during the clinical trial. The sponsor must investigate promptly, together with the investigator(s), all serious adverse events, take appropriate measures to ensure the safety of trial subjects, and report these events to appropriate authorities in accordance with applicable national requirements (see section 7).

5.14 *Termination of the trial*

If the sponsor elects or is required to terminate the clinical trial prematurely, then the investigator(s), ethics committee and relevant authorities must be notified of this decision, and of the reasons for termination.

6. Responsibilities of the monitor

The monitor is the principal communication link between the sponsor and the investigator and is appointed by the sponsor. The number of monitors needed to ensure adequate monitoring of the clinical trial will depend on its complexity and the types of centres involved.

The main responsibility of the monitor is to oversee progress of the trial and to ensure that the study is conducted and data are handled in accordance with the protocol, Good Clinical Practice, and applicable ethical and regulatory requirements. The monitor is responsible for

controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all subjects prior to their participation in the trial. Any unwarranted deviation from the protocol or any transgression of the principles embodied in Good Clinical Practice should be reported promptly to the sponsor and the relevant ethics committee(s).

The monitor should follow a predetermined written set of standard operating procedures (SOP). A written record should be kept of all visits, telephone calls and letters to the investigator.

6.1 *Qualifications*

The monitor should be appropriately trained and fully aware of all aspects of the drug under investigation and the requirements of the protocol, including any annexes and amendments. The monitor should have adequate medical, pharmaceutical and/or scientific qualifications, and clinical trial experience. The qualifications most appropriate for a monitor will depend on the type of trial and nature of the product under investigation.

6.2 *Assessment of the trial site*

The monitor should assess the trial site prior to the clinical trial to ensure that the facilities (including laboratories, equipment and staff) are adequate, and that an adequate number of trial subjects is likely to be available for the duration of the trial. The monitor should also assess the trial site during and after the trial to ensure that the investigator complies with the protocol and that data are handled in accordance with the predetermined set of standard operating procedures (SOP).

6.3 *Staff education and compliance*

The monitor should ensure that all staff assisting the investigator in the clinical trial have been adequately informed about and will comply with the details of the trial protocol.

6.4 *Data management*

The monitor should assist the investigator in reporting the data and results of the clinical trial to the sponsor, e.g. by providing guidance on correct procedures for completion of case-report forms (CRFs) and by verifying the accuracy of the data obtained (see also section 8).

6.5 *Case-report forms*

The monitor is responsible for ensuring that all case-report forms (CRFs) are correctly filled out in accordance with original observations. Any errors or omissions should be clarified with the investigator, corrected

and explained on the CRF. Procedures should be established for the investigator's certification of the accuracy of CRFs by a signature, initials or a similar method. All procedures for ensuring accuracy of CRFs must be maintained throughout the course of the clinical trial.

6.6 *Investigational product*

The monitor should confirm that procedures for the storage, dispensing and return of investigational product(s) are safe, adequate and properly documented in accordance with local regulations and the trial protocol (see also section 10.4).

6.7 *Communication*

The monitor should facilitate communication between the investigator and sponsor. The monitor (or some other responsible person designated by the sponsor and known to the investigator) should be available to the investigator at all times for reporting of adverse events or consultation on other trial-related matters.

6.8 *Notification of the trial or submission to the drug regulatory authority*

The monitor should assist the investigator in notifying the drug regulatory authority of the clinical trial and submitting any necessary documentation.

6.9 *Reports*

The monitor should submit a written report to the sponsor after each site visit and after all relevant telephone calls, letters and other contacts with the investigator. The report should include details of the findings and any actions taken.

7. Monitoring of safety

7.1 *Handling of and recording adverse events*

In accordance with sections 4.1 and 4.4 of these guidelines, the investigator must ensure the safety of the trial subjects. This includes providing the best possible care for subjects experiencing any trial-related adverse events and conducting a thorough investigation to determine causality.

The occurrence of adverse events must be monitored carefully and recorded in detail during the course of the clinical trial.

The trial protocol should clearly state the method(s) by which adverse events will be monitored. Provisions should be included to ensure prompt dose reduction or withdrawal of therapy for patients experiencing unacceptable toxic effects. The protocol should describe how information relating to adverse events is to be handled and analysed by the

investigator and the sponsor, and their responsibilities to report to each other and to the drug regulatory authority. The sponsor should provide special forms for reporting trial-related adverse events.

Consideration should be given to establishing a special committee to monitor adverse events (see also section 13).

7.2 *Reporting adverse events*

Regulations

National regulations vary considerably in their requirements for reporting adverse events. For serious events, however, accelerated reporting is required.

National regulations may require the sponsor and/or the investigator to report certain types of adverse events or reactions (e.g. serious, previously unknown) to the drug regulatory authority and ethics committee. If required, all such reports should be accompanied by an assessment of causality and possible impact on the clinical trial and on the future use of the product. In reporting, measures should be taken to avoid unnecessary duplication.

The investigator

The investigator must report serious adverse events to the sponsor immediately and to the drug regulatory authority and the ethics committee as specified in the protocol and in accordance with national regulations. Normally, adverse events associated with the use of the product must be reported to the drug regulatory authority within a specified time limit.

Reports on adverse events submitted by the investigator to the drug regulatory authority should contain both subject and trial identification data (i.e. the unique code number assigned to each subject in the trial).

When reporting adverse events to the sponsor, the investigator should protect confidentiality by excluding the names of individual subjects, personal identification numbers (e.g. social security numbers) or addresses. The unique code number assigned to the trial subject should be used in the report and the investigator should retain the code to facilitate verification of data by the sponsor or drug regulatory authority and any medical follow-up which may be warranted. The name of the investigator reporting the adverse events should be stated.

After the trial has been completed or terminated, all recorded adverse events should be listed, evaluated and discussed in the final report.

The sponsor

During the trial, the sponsor is responsible for reporting any trial-related adverse events or reactions associated with the use of the investigational product to the local health authority as required by national regulations and to other investigators involved in clinical trials of the same product.

The sponsor should also report as soon as possible to the investigator as well as to the drug regulatory authority and relevant authorities in other countries any trial with the same product that has been stopped due to action taken by a regulatory authority, or any other withdrawals of the product from the market for safety reasons. The sponsor should amend the investigator's brochure as required to keep the description of adverse events updated and to include any other significant new safety information.

8. Record-keeping and handling of data

The aim of record-keeping and handling of data is to record, store, transfer and, where necessary, convert efficiently and accurately the information gathered on each trial subject into data that can be used in the report.

All steps involved in data management should be documented in order to allow step-by-step retrospective assessment of the quality of the data and the performance of the clinical trial ("the audit paper trail concept"). Documentation is facilitated by methods such as the use of checklists and forms giving details of action taken, dates, the individuals responsible, etc.

The allocation of responsibilities for record-keeping and handling of data should be specified in the protocol or other written agreement(s) between the sponsor and investigator(s).

A basic aspect of the integrity of data is the safeguarding of "blinding" with regard to treatment assignment. It starts with the randomization of patients into treatment groups and is maintained through all steps of data processing up to the moment when the decision to break the code is formally taken.

In the event of electronic handling of data, confidentiality of the database must be secured by safety procedures such as passwords and written assurances from all staff involved. Provision must be made for the satisfactory maintenance of the database and for back-up procedures.

8.1 *Responsibilities of the investigator*

(a) The investigator has overall responsibility for ensuring the accuracy and completeness of data entry. The investigator must ensure that the observations and findings are recorded correctly and completely on the case-report forms (CRFs) and signed by the responsible person designated in the protocol.

When conducting a study and using CRFs to report clinical trial data to the sponsor, the investigator must also ensure that the routine requirements for recording of data in the source documents (e.g. hospital and laboratory records, consultation files) are met, particularly those relating to the treatment given to the subject and adverse events.

(b) If trial data are entered directly into a computer, there must always be an adequate safeguard to ensure validation, including a signed and dated printout and back-up records. Computerized systems should be validated and a detailed description for their use should be produced and kept up to date.

(c) All corrections to CRFs and to raw data must be made in a way which does not obscure the original entry. The correct data must be inserted with the reason for the correction (if not obvious), the date, and the initials of the investigator or authorized person. For electronic data processing, only authorized persons should be permitted to enter or modify data in the computer and there should be a record of changes and deletions. If data are altered during processing, the alteration must be documented.

(d) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, should always be recorded on the CRF or be attached to it. Values outside a clinically accepted reference range or values that differ significantly from previous values must be evaluated and commented upon by the investigator.

(e) Data other than those required by the protocol may appear on the CRF, provided they are clearly marked as additional or optional findings, with an explanation of their significance.

(f) Units of measurement must always be stated, and conversion of units must always be indicated and documented.

(g) The final report of the trial should be drawn up as defined in the protocol. The report should be signed by the sponsor, monitor and investigator(s), as well as by the responsible statistician, in accordance with the applicable regulations.

(h) For a period of time defined by national regulations, the investigator should maintain a confidential record to allow the translation of the code used to conceal the identity of the individual subjects in the trial (subject identification code). The investigator may submit the subject identification code list to the drug regulatory authority after the trial, together with the final report, according to national regulations.

(i) The investigator should ensure that the subject's participation in the clinical trial is clearly marked in his or her medical records.

8.2 *Responsibilities of the sponsor and the monitor*

(a) When electronic data handling or remote electronic data entry systems are employed, the sponsor must use validated data processing programs with adequate user documentation. A predetermined set of standard operating procedures (SOP) for such systems must be available. Such systems should be designed to allow correction after loading, and the corrections made must appear in an audit file.

(b) Appropriate measures should be taken by the monitor to avoid overlooking missing data or including inconsistencies. If a computer assigns values automatically when data are missing, this should be made clear.
(c) The sponsor must ensure the greatest possible accuracy when processing data. If data are transformed during processing, the transformation must be documented and the method validated. It should always be possible to compare the data printout with the original observations and findings.
(d) The sponsor must be able to identify all data entered pertaining to each subject by means of an unambiguous code.
(e) The sponsor must maintain a list of persons authorized to make corrections, and prevent unauthorized access to the data by appropriate security systems.

8.3 *Archiving of data*

As required by national regulations, the investigator must arrange for the retention of the subject identification codes for a sufficient period of time to permit any medical follow-up which may be warranted, including follow-up for delayed toxic reactions. It must be possible to identify each trial subject by name against the subject and product container identification codes, treatment assignment, and the CRFs. Subject files and other supporting data must be kept for a period of time as required by local regulations. The sponsor or supplier of the product must make appropriate arrangements for the retention of all other essential documentation pertaining to the clinical trial in a form which can be retrieved for future reference. Archived data may be kept on microfiche or electronic or optical record (e.g. compact disc), provided that a hard copy can be made available on request.

The protocol, documentation, approvals and all other essential documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out, must be retained by the sponsor. Data on adverse events must always be included.

All data and documents should be made available if requested by relevant authorities.

9. Statistics and calculations

The use of qualified biostatistical expertise is necessary before and throughout the entire clinical trial procedure, commencing with the design of the protocol and case-report forms (CRFs) and ending with completion of the final report and/or publication of the results.

The sponsor and the investigator should agree where and by whom the statistical work should be carried out. This information and the name of the responsible statistician should be recorded in the protocol.

9.1 *Experimental design*

The scientific integrity of a clinical trial and the credibility of the data produced depend primarily on the design of the trial. In the case of comparative trials, the protocol should therefore describe:

- an *a priori* rationale for the difference between treatments that the trial is designed to detect, and the statistical power to detect that difference, taking into account clinical and scientific information and professional judgement on the clinical significance of statistical differences;
- measures taken to avoid bias, particularly with regard to the randomization, when relevant, and selection of patients.

9.2 *Randomization and blinding*

In the case of a randomized clinical trial, the randomization procedure must be documented. Where a sealed code for each individual treatment has been supplied in a blinded, randomized study, it should be kept both at the site of the investigation and with the sponsor.

In the case of a blinded trial the protocol must state the conditions under which the code may be broken and by whom. A system is also required to enable immediate access to the information about treatment received by individual subjects in the case of an emergency. The system must only permit access to the treatment schedule of one trial subject at a time. If the code is broken, this must be justified and documented in the CRF.

9.3 *Statistical analysis*

The type(s) of statistical analyses to be used must be specified in the protocol, and any other subsequent deviations from this plan should be justified and described in the final report of the clinical trial. The statistical analysis should be planned and carried out or verified by an identified, appropriately qualified and experienced statistician. The possibility and circumstances of interim analyses must also be specified in the protocol.

The investigator and the monitor must ensure that the data are of the highest quality possible at the point of collection and the statistician must ensure the integrity of the data during processing.

The results of statistical analyses should be presented in such a manner as to facilitate interpretation of their clinical importance, e.g. as estimates of the magnitude of the treatment effect, the difference between treatments and confidence intervals, rather than in a form that relies solely on significance testing.

An account must be made of missing, unused or spurious data excluded during statistical analyses. All such exclusions must be documented so that they can be reviewed if necessary.

10. Handling of and accountability for pharmaceutical products

The sponsor is responsible for ensuring that the investigational pharmaceutical product(s) and, if applicable, comparator products supplied for the clinical trial are of appropriate quality and subject to quality assurance procedures (see section 5.11).

If significant changes are made in the formulation of the investigational or comparator product during the course of the trial, the results of additional studies (e.g. on the stability, comparative dissolution rate or, as appropriate, comparative bioavailability) should be made available before the new formulation is used in the trial. The studies should demonstrate that the changes would not be expected to alter the pharmacokinetic profile or other clinical characteristics of the product.

10.1 *Supply and storage*

The arrangements made by the sponsor to supply the investigator with pharmaceutical products for the clinical trial should be described in the protocol. The manner in which the study products are to be recorded, delivered, dispensed and stored should be detailed.

The principles of Good Manufacturing Practice (*1*) should be applied not only by the supplier of the pharmaceutical product(s), but also by any intermediaries responsible for storing the product(s) temporarily.

Records must be kept of information about the shipment, delivery, receipt, storage, return and destruction of any remaining pharmaceutical products. The investigator should not supply the investigational product to any person not targeted to receive it. Preferably a local pharmacy or the pharmacy department of the local hospital should assume responsibility for storage, delivery, return and keeping records of the investigational and, when appropriate, comparator product(s). If so, these procedures must be documented to make auditing possible.

10.2 *Investigational labelling and packaging*

The sponsor is responsible for the proper packaging and investigational labelling of the pharmaceutical products used. Study products should be labelled in compliance with the protocol and any applicable national regulations. The investigational label should state that the product is for clinical research purposes only. Investigational label information should be accurate and in a language that is understandable to the subject.

In blinded trials, the package should be labelled in a way that does not reveal the identity of the product. A coding system should be used to allow for the proper identification of the blinded products given to individual subjects (in case of emergency). In addition, all study products, including comparator products, should be indistinguishable by appearance, taste, smell, weight and other physical characteristics.

10.3 *Responsibilities of the investigator*

The investigator is responsible for ensuring:

- Proper and safe handling of the investigational and, when appropriate, comparator products during and after the clinical trial, preferably in cooperation with a pharmacy (see section 10.1).
- That the investigational product is used in accordance with the protocol, which implies use only for subjects included in the trial and by designated staff responsible to the investigator, and that this use is documented in such a way as to ensure appropriate dosage.
- That the dosage and instructions for use are correct and that every subject involved understands them properly.
- That unused investigational and, when appropriate, comparator products are returned in accordance with the protocol to the pharmacy or sponsor or destroyed, and that proper records of these activities are kept.

10.4 *Responsibilities of the sponsor and the monitor*[1]

The sponsor is responsible for:

- Supplying the investigational and, when appropriate, comparator product(s), prepared in accordance with principles of Good Manufacturing Practice. The products should be fully characterized, properly coded, and suitably packaged in such a way as to provide protection against deterioration during transport and storage at intermediate destinations; appropriate investigational labelling should be affixed (see section 10.2).
- Ensuring that the package of investigational product(s) is of a size suitable for the clinical trial and adequate for the trial subjects.
- Keeping sufficient samples from each batch used in the trial as a reference for control tests and validation of data, as required by national regulations.
- Providing information about the expiry date (month/year) or retest date in a manner understandable to all staff involved in the trial.

During the visits to the clinical trial site, the monitor should check:

- That all study products for the trial are used exclusively within the limits defined by the protocol.
- That inventory records of study products are in order and that there are sufficient supplies.
- That the expiry dates of the products are not likely to be, or have not been, exceeded.
- That the storage conditions for study products are adequate.
- Procedures for and records of returned and/or unused study products.

[1] See also sections 5 and 6.

11. Role of the drug regulatory authority

The role of governments is to provide the legal framework for clinical trials. The aim should be twofold: (i) to protect the safety and rights of the subjects participating in a trial, and (ii) to ensure that trials are adequately designed to meet scientifically sound objectives. These aims may be met by several means, including the specification of the investigator's qualifications and requirement for review and approval of the protocol by relevant scientific and/or ethics committees.

Drug regulatory authorities should have a mandate to review protocols and, where necessary to protect the safety of subjects, to require protocol revisions and/or termination of trials.

Regulations should allow for on-site inspections of the quality and reliability of the data obtained, with due concern for confidentiality.

11.1 *General responsibilities*

The national drug regulatory authority should ensure that the protocols for clinical trials are submitted in advance for review and are in accordance with existing national regulations. On the basis of its review of clinical trial protocols and/or reports, the regulatory authority may propose revisions to a protocol, request additional data or terminate a trial.

The drug regulatory authority should evaluate the adequacy of supervision of the trial by reviewing the monitor's reports to the sponsor (see section 6.9). In addition, the authority should be able to conduct on-site inspections of the reliability and quality of reported results.

National regulations should specify the procedures for reporting and handling cases of misconduct discovered in connection with clinical trials.

11.2 *On-site inspections*

As permitted by national regulations, the drug regulatory authority may carry out on-site inspections of the clinical trial site. Such inspections may be carried out routinely, randomly and/or for specific reasons, and should consist of a comparison of the procedures and practices of the investigator with those set out in the protocol and reports submitted to the regulatory authority by the investigator or the sponsor.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The data archives should be tested for ease of retrieval.

Inspections may include data audit. The drug regulatory authority should have easy access to all patient files and raw data used for and generated during the trial.

12. Quality assurance for the conduct of a clinical trial

The sponsor is responsible for implementing a system of quality assurance to ensure that the trial is performed and the data are generated, recorded and reported in compliance with the protocol, Good Clinical Practice and national regulations.

All clinical trial sites, data and documents must be available for verification. All observations and findings should be verifiable in order to ensure the credibility of data and to assure that the conclusions presented are derived correctly from the raw data. The verification processes must be specified and scientifically justified. Statistically controlled sampling may be used to verify data obtained in a trial.

Quality control procedures must be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The sponsor, investigational sites, facilities and laboratories, and all relevant data (including raw data) and documentation and reports concerning the data (including subject files) must be available for an audit and for inspection by relevant health authorities. The audit should be conducted by a nominated person(s) or organization(s) independent of those carrying out the clinical trial.

13. Considerations for multicentre trials

Because a multicentre clinical trial is conducted simultaneously by several investigators at different sites following the same protocol, some special administrative arrangements are normally needed. Ideally, the trial should begin and end simultaneously at all sites.

A number of aspects are rendered more complex in multicentre trials, such as:

- the elaboration, discussion and written acceptance of the protocol and its annexes by all investigators;
- submission of the proposed protocol or protocol amendments to the ethics committee(s), and the number of committees to be consulted;
- the organization of initial and intermediary meetings of parties involved in the trial;
- implementation of the trial;
- the procedure(s) used for the randomization of trial subjects;
- ensuring that the quality of the investigational and comparator products, if used, is maintained during distribution and storage in different locations;
- the training of investigators to follow the same protocol;
- standardization of methods for evaluating and analysing laboratory and diagnostic data (e.g. establishment of an external quality-control system for laboratory assays);
- control of adherence to the protocol, including measures to terminate participation of trial sites if necessary;

- the role of the monitor(s);
- centralized data management and analysis;
- drafting of the final report and clearances required;
- publication of the trial results.

A multicentre trial therefore may require a special administrative system, the scale of which will depend on the number of trial sites involved, study end-points and knowledge of the investigational pharmaceutical product. One or several committees may be set up for this purpose or the necessary functions may be performed by one or more designated person(s). The functions, responsibilities and mandate of the committee(s) or person(s) should be described in the trial protocol, as should the procedure for nomination.

For example, a committee or an individual could be responsible for overseeing the initiation and overall performance of the trial. Similarly, a second committee or person could be appointed to provide advice on policy matters and data collection. A third committee or person could be made responsible for the accuracy and verification of the data obtained. This committee or person would therefore require access to the results obtained in the trial, including adverse events. It should be stated in the protocol under what circumstances and how this committee or person can break the trial code. Collaboration between these committee(s) or person(s) is necessary.

A coordinating committee could also be set up or a coordinator appointed with responsibility for the control of the performance and progress of the trial and maintaining contacts with the drug regulatory authorities and ethics committees.

These administrative arrangements will provide adequate assurance that the study will be planned and conducted according to generally accepted scientific principles and Good Clinical Practice.

References

1. Good manufacturing practices for pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823), Annex 1.

2. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Geneva, CIOMS, 1993, Annex 1.

Appendix 1
Declaration of Helsinki[1]

Recommendations guiding physicians in biomedical research involving human subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a

[1] Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, Hong Kong, September 1989. **World Medical Association.** *Handbook of declarations.* Ferney-Voltaire, 1992 (unpublished document; available on request from the World Medical Association, 28 avenue des Alpes, 01210 Ferney Voltaire, France).

guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix 2
Model list of items to be included in a clinical trial protocol

The clinical trial protocol should, where relevant, be required to cover the following points:

1. Title and justification for the trial.
2. Statement of the rationale, objectives and purpose of the trial.
3. Brief description of the site(s) where the trial is to be conducted.
4. Name and address of the sponsor.
5. Name, address and qualifications of each investigator.
6. Detailed description of the type of trial (randomized, blinded, open), trial design (parallel groups, cross-over technique), blinding technique (double-blind, single-blind), and method of and procedure(s) for randomization.
7. Description of the trial subjects (criteria for inclusion and exclusion of potential subjects), process of recruitment, and method(s) and timing of allocation of subjects into investigational groups.
8. Number of trial subjects needed to achieve the trial objective, based on statistical considerations.
9. Description of and justification for the route of administration, dosage, dosage interval and treatment period for the investigational and comparator products, if used. Dose-response relationships should be considered.
10. Any other treatment that may be given or permitted concomitantly.
11. Clinical and laboratory tests, pharmacokinetic analyses, etc., that are to be carried out.
12. Description of how responses are to be recorded (description and evaluation of methods and frequency of measurement), follow-up procedures, and measures to determine the extent of compliance with the treatment among trial subjects.
13. Discontinuation criteria for trial subjects and instructions on terminating the whole study or a part of the study.
14. Methods for recording and reporting adverse events or reactions, and provisions for dealing with complications.
15. Procedures for the maintenance of subject identification code lists, treatment records, lists for the randomization of subjects and/or case-report forms (CRFs). Records should permit identification of individual patients or participants as well as auditing and reconstruction of data.

16. Information about how the trial code is established, where it will be kept, and when, how and by whom it can be broken in the event of an emergency.
17. Measures to be implemented to ensure the safe handling and storage of the investigational and comparator products, if used, and to promote and determine the extent of compliance with the prescribed treatment and other instructions.
18. Description of the methodology to be used to evaluate the results (including statistical methods) and to report on patients or participants withdrawn from the trial.
19. Time schedule for completion of the trial.
20. Information to be presented to the trial subjects, including how they will be informed about the trial, and how and when their consent will be obtained.
21. Instructions for staff involved in the trial, including how they are to be informed about the way the trial is to be conducted and about the procedures for drug usage and administration.
22. Ethical considerations and measures relating to the trial.
23. Medical care to be provided after the trial, and modalities of post-trial treatment.
24. When the protocol serves as a contract, statements regarding financing, insurance, liability, delegation or distribution of responsibilities, and publication policy.
25. List of literature referred to in the protocol.

Annex 4
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.