NB: Important Notice

This is the text of the report as it was written and approved by the WHO Expert Committee on the Selection and Use of Essential Medicines at its meeting in Geneva from 31 March to 3 April 2003. Approval for publication of the report was given by the WHO Director-General. Language editing and proof reading of the text will take place before its final publication in the WHO Technical Report Series.

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2003

(including the 13th Model List of Essential Medicines)

World Health Organization

Geneva, 2003

Disclaimers

List of contents

Introduction 6
Update on current activities 8
Report of the *ad hoc* Advisory Committee on priority vaccines 10
Applications for addition 12
Applications for deletion 22
Application for addition of information 26
Applications for change 27
Fast-track procedure for deletion 30
Review of Core and Complementary Listing 33
Review of use of Square Box Symbol 36
Review of section 12.3 Antihypertensive medicines 41
Priorities for review 43
Review of activities to promote rational drug use 46
Summary of recommendations: 50
Annexes: 55

WHO Expert Committee on the Selection and Use of Essential Medicines

Geneva, 31 March - 3 April 2003

Members

Professor P. M. de Buschiazzo, Department of Pharmacology, School of Medicine, University of La Plata, Argentina

Professor A. Helali, Director, Centre National de Pharmacovigilance et Matériovigilance, Ministère de la Santé et de la Population, Algeria

Professor R. Laing, Boston University, School of Public Health, USA

Professor J-R Laporte, Department of Pharmacology and Therapeutics, Fundacio Institut Català de Farmacologia, Universitat Autonoma de Barcelona, Spain (*Chairman)*

Professor D. Ofori-Adjei, Director, Noguchi Memorial Institute for Medical Research, University of Ghana, Ghana

Dr E.M.A. Ombaka, Director, The Pharmaceutical Programme of Community Initiatives Support Services, World Council of Churches, Kenya

Dr M. M. Reidenberg, Chief, Division of Clinical Pharmacology, The New York Hospital-Cornell Medical Centre, USA (*Vice-Chairman*)

Professor S. Suryawati, Centre for Clinical Pharmacology and Drug Policy Studies, Gadjah Mada University, Indonesia (*Rapporteur)*

Dr L. Wannmacher, Department of Clinical Pharmacology, School of Medicine, University of Passo Fundo, Brazil

Temporary Advisers

Professor U. Gupta, Delhi Society for Promotion of Rational Use Of Drugs (DSPRUD), India

Dr S. Hill, Faculty of Medicine and Health Sciences, University of Newcastle, Mater Misericordiae Hospital, Australia

Dr Y. Li, Chinese Cochrane Centre, West China Hospital, Sichuan University, China

Mr D. K. Mehta, Executive Editor, British National Formulary, Royal Pharmaceutical Society, United Kingdom

Dr L. Offerhaus, Netherlands

Mr A. Pillay, Faculty of Medicine & Health Sciences, University of Newcastle, Mater Misericordiae Hospital, Australia

Mr P. J. Wiffen, The Cochrane Collaboration, Pain, Palliative & Supportive Care CRG (PaPaS), Pain Research Unit, Churchill Hospital, United Kingdom

Professor L. E. Ziganshina, Kazan State Medical University, Dept of Clinical Pharmacology and Pharmacotherapy, Russia

Representatives from other organizations*

International Paediatric Association (IPA)
Professor T. I. Bhutta, Pakistan

WHO Collaborating Centre for International Drug Monitoring
Professor C. van Boxtel, The Netherlands

United Nations Children's Fund (UNICEF)
Ms T. H. Ha, Technical Officer, Supply Division, Denmark
Mr Mark W. Young, Senior Health Advisor, New York Headquarters, USA

Joint United Nations Programme on HIV/AIDS (UNAIDS)
Dr F. Renaud-Théry, Care & Support Network Adviser, Geneva, Switzerland

United Nations Population Fund (UNFPA/CST)
Dr G. Walker, Specialist in Reproductive Health Commodities, Bratislava

The World Bank
Unable to send a representative

Secretariat

Dr A. Asamoa-Baah, Executive Director, Health Technology and Pharmaceuticals, WHO, Geneva, Switzerland

Dr J. D. Quick, Director, Essential Drugs and Medicines Policy (EDM), WHO, Geneva, Switzerland

Dr H. V. Hogerzeil, Coordinator for Policy, Access and Rational Use (PAR)/EDM, WHO, Geneva, Switzerland (*Secretary)*

Dr R. C. F. Gray, Medical Officer, Policy, Access and Rational Use (PAR)/EDM, WHO, Geneva, Switzerland

Introduction

The WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 31 March to 3 April 2003. The meeting was opened on behalf of the Director-General by Dr J. D. Quick, Director of the Department of Essential Drugs and Medicines Policy. After welcoming the participants he expressed appreciation for the rapid dissemination of the report of the previous meeting and the first issue of the WHO Model Formulary in 2002. He referred to the recent 25th anniversary of the essential medicines concept and stressed that the global relevance of the concept is now generally accepted; but that still many challenges remain, especially with regard to ensuring equitable access to essential medicines.

After the election of officers, the WHO Secretariat requested agreement from the Committee to hold an open session as part of its meeting (see section 2). The reason for the open session was to allow all stakeholders to participate in discussions and comment on issues relating to the WHO Model List of Essential Medicines. For Expert Committee members it created an opportunity to receive at first-hand additional information and opinions on matters under consideration. Participants were assured that the discussions and considerations of the open session would be reflected in the report of the meeting. A summary of the Committee's meeting report would be submitted to the WHO Executive Board in January 2004, together with a statement on the public health implications of its recommendations. The Committee agreed to hold an open session.

The Committee decided to maintain the format decided upon in the previous year. The updated version of the Model List and explanatory notes are presented as Annex 1 to this Report.

Open session

The open session was opened by Dr A. Asamoa-Baah, Executive Director of the Health Technology and Pharmaceuticals cluster. He reported that WHO is proud of the success of the essential medicines concept, as evidenced at the recent 25th anniversary. He stressed that the careful selection of essential medicines for the WHO Model List are the core of the programme, as they constitute the moral basis for national drug policies and the technical basis for procurement, quality assurance and promoting rational use of medicines. In that respect, the future of the essential medicines programme depends on the credibility of the work of this Expert Committee. And this credibility, in turn, depends very much on the new procedures as

they have been introduced recently. He went on to remind participants that all their comments would be noted and that final recommendations on each of the agenda items would be formulated in the light of these comments in subsequent private sessions of the Committee.

In the open session, an update was presented on the current activities related to the Model List (see below) and an overview of the procedures for fast-track deletion, definition of the core and complementary lists, and the use of the square-box symbol. Comments made at the open session were noted and are reported under the respective agenda item.

In addition to comments on agenda items, and as previously, the International Federation of Pharmaceutical Manufacturing Associations made a statement of concern about the lack of transparency in the EDL decision-making process, in part related to the way members of the Committee are selected. Potential conflicts of interest should be publicized and applied to all members of the Committee, including special advisors. The breadth of expertise should also be expanded. Technical advice from industry has not been effectively sought in preparation for the meeting and industry's expertise has been excluded from this Committee's deliberations. IFPMA welcomes WHO's efforts to the provision of quality drugs through the new prequalification system. However, he cautioned against the promotion of untested fixed-dose regimens, such as some combinations of antiretroviral medicines that may actually harm patients.

A representative of the US mission expressed satisfaction with the principle of the open session, and requested that this be established as a permanent part of the procedure. He also stressed the need for the Committee to have permanent access to expertise in drug regulation and quality assurance.

In the discussion the Committee noted that in the case of tuberculosis, the advice of WHO had led to a full standardisation of the dosage of fixed-dose combinations, which was now followed by most manufacturing industries. The WHO clinical guidelines for the treatment of HIV/AIDS with antiretroviral therapy would serve the same purpose. The Committee also noted the lack of technical contributions by pharmaceutical companies despite posting on the web site all applications and systematic reviews well in advance of the meeting. With regard to the conflict of interest by members of the Committee, the Secretary explained the standard procedure for declarations of interest, which is rigorously applied. Dr Asamoa-Baah added that the credibility of the Committee is also, to a large extent, derived from the scientific basis and transparency of its recommendations.

Update on current activities

Dissemination of the Report of the 12th Expert Committee

After approval of its report by the Expert Committee on Friday 19 April 2002, the report was approved for publication by the Director-General and published on the WHO web site on Monday 22 April, ten working hours after the meeting was closed. The rapid dissemination of the report, the updated Model List and the summary of recommendations was widely appreciated, especially in view of the important recommendations the Committee had made on the selection of essential medicines for HIV/AIDS and malaria.

The 12th Model List and the general introductory text, as presented in Annex 1 of the full report, were translated into Arabic, Chinese, French, Russian and Spanish and published on the web within weeks of the meeting. These web pages in the six official languages of WHO were also disseminated in large numbers on paper. The full report was edited for publication in the Technical Report Series. However, the separation of the core and complementary lists and the introduction of the ATC classification lead to some delay. The numbering of the various committee meetings and reports had been confusing in the past, mainly due to changes in the name of the Expert Committee. For the sake of clarity it was decided to use the numbering system of the Model List.

In January 2002, a summary of the report and a statement on its public health implications were submitted to the WHO Executive Board. The 12th Model List was also included in the WHO Essential Medicines Library (see below).

25th Anniversary of Model List of Essential Medicines

On 21 October 2002 exactly 25 years since the first Expert Committee approved the first Model List of Essential Medicines, a technical seminar in Geneva celebrated the achievements of the global application of the concept of essential medicines. On the same day, regional anniversary seminars were also held in Cambodia and Brazil. All presentations, including an important speech by the Director-General, were published on the WHO/EDM web site (www.who.int/medicines) and is available on CD-ROM.

WHO Model Formulary

After the Expert Committee meeting in 2002, additional entries were prepared for the antiretroviral medicines and other new inclusions in the 12th Model List, in order to make the first Model Formulary fully compatible with the latest Model List. The Formulary was launched at the annual congress of the International Pharmaceutical Federation in Nice, in September 2002, and was generally very well received. The first print of 7,000 copies have all been distributed, both by free distribution and through commercial channels; a second printing was ordered in November 2002. A searchable version is on the WHO medicines web site. A CD-ROM, for use by national and institutional committees, is nearing completion. Agreement has been reached with the British National Formulary for editing and printing future versions of the Model Formulary.

Review of New Emergency Health Kit

The 55 essential medicines listed in the New Emergency Health Kit[1] are all included in the list of 88 medicines recommended for emergency relief by the UN[2]; and all of these are included in the Model List. Following a consultation with the partners involved in the New Emergency Health Kit it was decided that this kit needs to be updated, especially for the antimalarial medicines, oral rehydration salts, emergency contraception and injection materials. The review meeting will be convened by WHO in autumn 2003.

[1] The New Emergency Health Kit. Drugs and medical supplies for 10,000 for approximately 3 months. Geneva: WHO, 1998; WHO/DAP/98.10 (Interagency document in English, French, Russian and Spanish).

[2] Emergency Relief Items - Compendium of basic specifications, Volume 2. New York: UNDP/IAPSO, 1999

Review of essential medicines for reproductive health

It was noted that the draft inter-agency list of essential medicines for reproductive health and the UNFPA core list of essential medicines for reproductive health are not fully consistent with the Model List. For example, 22 items on the inter-agency list and 6 medicines on the UNFPA list do not appear on the Model List. A review is being undertaken to analyse these discrepancies, and to collect and review the clinical guidelines and evidence which support the selected items on the other lists. This evidence will be used to streamline the three different lists; the information will also be included in the Essential Medicines Library.

Report of the *ad hoc* Advisory Committee on priority vaccines

Following a recommendation of the Strategic Advisory Group of Experts (SAGE) in 2002 to "*establish an expert advisory committee with worldwide representation to develop a mechanism for prioritisation of vaccines for a model essential vaccine list for immunisation programmes*", an *ad hoc* Advisory Committee was convened to address this issue. The Advisory Committee agreed that national lists of essential vaccines should be established and that the construction of such lists could be facilitated by the creation of a Global Model List of Essential Vaccines as well as an Evidence-based Library of Essential Vaccines. The Committee felt that since there are fundamental differences between medicines and vaccines, an evidence-based Model List of Essential Vaccines should be separate from the Model List of Essential Medicines. Once the new list is established, vaccines should be taken off the Essential Medicines List, although the two lists should refer to each other. In making the new list, the traditional children's vaccines will remain listed but all other vaccines will be subjected to evaluation by an Expert Committee before inclusion. A procedure similar to that used for essential medicines may be followed.

The Advisory Committee also felt that while a WHO Model List of Essential Vaccines may be prepared, the emphasis should remain on the development of national and/or regional lists, using the information provided in the essential vaccines library. The Advisory Committee therefore also recommended that criteria for prioritizing vaccines for inclusion in national lists be developed. A first list of such criteria was prepared, to be subjected to external review and tested before use. The recommendations of the Advisory Committee will be presented to SAGE in July 2003.

WHO Essential Medicines Library

Work on the WHO Essential Medicines Library is continuing. In its current public version it contains searchable versions of the 12th Model List and the WHO Model Formulary, and a link to the MSH Drug Price Indicator Guide and the WHO Collaborating Centre on drug statistics methodology in Oslo. In the developmental version, a central "Medicine link page" is prepared for each item on the Model List, which presents the INN, dosage(s), ATC number(s), justification for inclusion, and links to key indications, disease summaries, systematic reviews and WHO clinical guidelines. There are links to the WHO Model List, the WHO Model Formulary and the INN web site and to external web sites with the MSH Drug Price Indicator Guide and the ATC/DDD classification,. It is expected that the developmental version will be opened to the public in the course of 2003.

Applications for addition

Amodiaquine

The Committee reviewed the re-application for the inclusion of amodiaquine after the deferral of a decision at its last meeting. Amodiaquine has been on the Model List since 1977, was removed in 1979, reinstated in 1983 and removed again in 1988 in view of safety concerns in prophylactic use. In 2002 the Committee had reviewed an application for inclusion for therapeutic use. However, as amodiaquine had been removed twice for safety reasons the Committee considered at that time that a careful review of the safety information was needed before it could decide to add it again to the Model List. The Committee had noted with concern the results of a trial of amodiaquine in children that appeared to show a high rate of neutropenia.

The Committee noted the information supplied with the re-application, a systematic review of adverse events prepared by the Cochrane Infectious Diseases Group and the review on white blood cell and neutrophil counts following amodiaquine treatment presented by the WHO Malaria department. In addition, other publications reviewed[3,4] suggest that peripheral neutropenia is a part of the natural course of malaria itself. The Committee concluded that antimalarial drug treatment with amodiaquine, (either alone or combined with sulfadoxine/pyrimethamine or artesunate), chloroquine and sulfadoxine/pyrimethamine may be associated with a decline in the total white cell and neutrophil counts. The majority of these counts are in the normal range but small proportions of patients have developed neutropenia when assessed during follow up. The clinical significance of this finding is unknown.

The Committee concluded that these analyses support the conclusions of the systematic review of adverse events prepared by the Cochrane Group that therapeutic use of amodiaquine does not appear to be associated with an increased risk of neutropenia compared to other commonly used antimalarial drugs. The Committee recommended that amodiaquine tablet, 153 mg or 200 mg (base) be added to the core list and its recommended place in curative treatment be further defined by WHO guidelines, that the following note be added: "*amodiaquine should preferably be used as part of combination therapy*" and that the following text be added at the heading of the section:

[3] Church LWP et al. Clinical manifestations of P. falciparum malaria experimentally induced by mosquito challenge. J. Infect Dis 1997, 175: 915-920

[4] Dale DC, Wolff SM. Studies of the neutropenia of acute malaria. Blood 1973; 41:197

"Medicines for the treatment of *P. falciparum* malaria cases should be used in combination."

The Committee also expressed an interest in reviewing the results of more clinical trials on the comparative efficacy and safety of fixed-dose combinations in the treatment of malaria.

Azithromycin

The Committee reviewed two applications for the addition of azithromycin. One application was submitted by Médecins sans Frontières for listing as an individual medicine on the core list, for the treatment of chlamydial infection and trachoma; and one application from the WHO Department of Reproductive Health and Research as an individual medicine on the core list, for the treatment of genital chlamydia. The MSF application was reviewed and supported by the Department of Reproductive Health and Research.

The Committee noted that azithromycin, a macrolide antibiotic, has antimicrobial activity against a wide variety of microbes. Its effectiveness against C. trachomatis genital infection with a single dose has been shown in studies cited in the applications. It is safe for growing adolescents and for the fetus in a treated pregnant woman (reports cited in application), both at risk with a tetracycline, the alternative choice. The Committee noted that the safety of this drug in these sections of the population along with the advantages of single dose curative therapy support the selection of azithromycin for this disease.

The MSF application cited studies in which oral azithromycin was as effective in trachoma as antibiotic ointments. The Committee noted that there is an advantage of single oral dose treatment of an infection, especially when it is directly observed, over a prolonged course of prescribed medication.

The Committee therefore recommended that azithromycin 250 or 500mg capsule, and suspension 200mg/5ml be added to the core list, for the single dose treatment of genital C.trachomatis infection and of trachoma only. This recommendation was made in view of its effectiveness and safety as documented in the applications, and because of its ease of use when compared to the common alternatives (doxycycline twice daily for a week, or tetracycline ophthalmic ointment for 6 weeks). The Committee recommended that the following footnote be added: "*Only listed for single dose treatment of genital C.trachomatis and of trachoma.*"

Ibuprofen paediatric formulation

The Committee reviewed an application by Boots Healthcare International to add a paediatric formulation of ibuprofen on the core list. Comments on this application were received from the WHO Department of Child and Adolescent Health, UNICEF and the Cochrane Pain Research Group.[5]

The Committee noted that the application makes reference to evidence on the antipyretic effect of ibuprofen and proposes the use of ibuprofen suspension and suppositories in children younger than twelve years. Ibuprofen is used in the management of mild to moderate pain and inflammation but this latter property is weaker than the analgesic effect. The Committee reviewed the evidence submitted on the efficacy and effectiveness of ibuprofen as an antipyretic agent.

The Committee noted that the application was not complete and that important information on efficacy, safety and cost in relation to the antipyretic effect was missing. The application did not constitute a systematic review about the subject and confounding variables such as age, bacterial infection and positive culture and antimicrobial therapy before taking the antipyretic drug were not always taken into account.

The Committee noted that there was insufficient evidence to conclude that ibuprofen provides a better antipyretic effect than paracetamol, and that no evidence was supplied on the comparative safety of ibuprofen and paracetamol. No data on cost-effectiveness in comparison with paracetamol were provided either. On these grounds the Committee recommended that the current application be rejected, although it would consider a re-application in the required format and providing the information mentioned above. In considering the use of paracetamol in adults, the Committee recommended that a note be added to the current Model List to state that paracetamol, although listed in section 2.1 (Non-opioid analgesics and antipyretics and nonsteroidal anti-inflammatory drugs) was not recommended for anti-inflammatory use, due to lack of proven benefit to that effect.

[5] The full application and the comments are posted on the EDM web site and in the Essential Medicines Library.

Insulin semilente

An application was received from the Patient Association for the Preservation of Natural Animal Insulin Switzerland, the Insulin Forum Switzerland, the Insulin Independent Diabetes Trust International and the Swiss Tropical Institute in Basle, for the inclusion of intermediate amorphous (100%) porcine insulin suspension (insulin "semilente"). Comments on the application were received from the WHO Diabetes Team.

The Committee noted that the current Model List includes an intermediate-acting and a short-acting (soluble) insulin, but that the origin (human or animal) or the type (zinc suspension or isophane insulin) are not specified. The application for inclusion is based on the following reasons:

- It has more favourable pharmacokinetic properties than other intermediate-acting insulins and the incidence of nocturnal hypoglycaemia and early morning hyperglycaemia is lower
- It is the only prompt intermediate-acting insulin with added zinc ions and not bound to fish protamine
- Human insulins were introduced without any proof of superiority compared to animal insulins
- Some patients could present loss of hypoglycaemia warning symptoms after transfer to human insulin
- Animal insulins are cheaper than the corresponding human insulin.

The Committee noted that several aspects regarding the introduction of human insulin deserve attention. It was introduced without any proof that it is less immunogenic than animal insulins; the number of patients included in randomised trials has been limited (2,156 in the relevant Cochrane review); the mean duration of studies has been short (5.8 months); and the frequency of insulin resistance has not been assessed. Furthermore, transfer to human insulin has been associated with a higher risk of severe hypoglycaemia in some studies but not in others. In the Cochrane review the frequency of hypoglycaemic episodes with both types of insulins was similar.

The Committee noted the conclusion of the 2002 Cochrane review that there was no clinically relevant differences between animal and human insulin[6] and concluded that the selection between the two types should be made on the basis of cost. The Committee noted that intermediate acting insulin was already on the list and concluded that insufficient evidence was presented to justify a decision to single out any species-specific insulin.

[6] Richeter B, Neises G. "Human" insulin vesus animal insulin in people with diabetes mellitus. In the Cochrane Library, Issue 1, 2003 (Oxford, Update Software)

Miconazole buccal tablet (re-application)

An application was received through the WHO Cluster of Family and Community Health, to add to the Model List miconazole nitrate buccal tablets for the treatment of oropharyngeal and oesophageal candidiasis.[7] At its previous meeting in April 2002, a similar application had been reviewed. At that time the Committee had concluded that miconazole ointment or cream was already on the Model List; and that no comparison had been made between miconazole buccal tablets and nystatin lozenges.

The Committee reviewed the evidence presented and concluded that the efficacy of miconazole buccal tablet is no worse than that of ketoconazole given systemically and nystatin used locally. The committee also noted that adverse effects were rarely reported, on an estimated 552,381 patient exposure world-wide. Assuming therapeutic equivalence, the appropriate economic evaluation would be a cost-minimisation analysis, comparing treatment with miconazole buccal tablets, ketoconazole tablets and nystatin. The total cost for 100 patients was similar for miconazole nitrate and ketoconazole, with a higher cost for nystatin. In the secondary analysis the cumulative costs at week 3 were approximately one-third less in miconazole treated patients compared to the ketoconazole and nystatin treated patients.

The Committee noted that adequate comparison of effectiveness between miconazole formulations and nystatin formulations was not presented; that no safety data were submitted of miconazole buccal tablets in comparison with nystatin; that evidence was not provided on clinical benefit arising from possibly improved adherence to treatment; and that the application was not specifically supported by the WHO FCH cluster. The Committee therefore recommended that the application be rejected.

[7] The full application and the comments are posted on the EDM web site and in the Essential Medicines Library.

Misoprostol

An application was received from the Department of Obstetrics and Gynaecology of Medical School, Makarere University, Kampala, Uganda, to include misoprostol for obstetric and gynaecological indications.

The Committee noted that a synthetic prostaglandin E1 analogue – misoprostol – is only approved for prevention and treatment of NSAID-associated peptic ulcers although a 25 microgram vaginal tablet has been registered for hospital use in Brasil.[8] However, misoprostol has been extensively studied and widely used for obstetric and gynaecological indications, such as pre-induction cervical ripening (3rd trimester), labour induction (3rd trimester, especially at low Bishop scores), evacuation of the uterus after pregnancy failure or for various medical reasons (2nd trimester) and primary postpartum haemorrhage. It has been shown to be an effective myometrial stimulant of the pregnant uterus, even at the beginning of pregnancy. Thus, it is also an effective abortive agent. The concern about its widespread use as a self-medication has justified the non-approval for marketing in various countries, mainly where the abortion is considered illegal. For example, the use of misoprostol for obstetric indications is not approved of the *US Food and Drug Administration* (FDA).

The Committee noted the limited registration for obstetric and gynaecological indications and decided that this application therefore could not be considered at this meeting. If more widespread registration is achieved, a full application supported by a review of evidence on efficacy and safety would be considered.

[8] Agência Nacional de Vigilância Sanitária. Resolução RE nº 905, de 21 de junho de 2001. Publicado no DOU de 22/6/2001. http://www.anvisa.gov.br/anvisalegis/resol/905

Valaciclovir

An application was received from the WHO Department of Reproductive Health and Research to include valaciclovir on the Model List as a better example of a therapeutic group than aciclovir already listed, because it has better bioavailability and can be administered as a twice daily dose rather than the 4 to 6 times per day required for aciclovir. In the treatment of sexually transmitted infections, compliance is a key issue in ensuring the effectiveness of treatments. Successful treatment is also important for reducing the transmission of HIV and in promoting the credibility and acceptance of the syndromic approach to treatment.

The Committee noted that the application presented a comprehensive review of efficacy and safety studies that compare valaciclovir with aciclovir. The studies compare the two drugs as treatments for the first clinical episode of genital herpes or as treatment for recurrent infections or as suppressive therapy, presenting the dosage regimen for each indication.

The Committee noted that none of the randomised controlled trials and reviews of comparative effectiveness of valaciclovir and acyclovir show significant differences between the two and that both are effective when compared to placebo. None of the trials report adherence to treatment or patient preferences as an outcome measure. In addition, the treatment regimens for some of the indications involve twice-daily dosing for both drugs.

On the basis of the assessment of comparative clinical performance and lack of evidence of benefit from better adherence to treatment, the appropriate approach to an economic evaluation would be a cost minimisation evaluation. The cost per course of 5 days treatment with aciclovir ranged from US$ 1.46 to US$ 31.69. The cost per course of 5 days treatment with valaciclovir is US$ 36.72. The only way such a cost differential could be justified would be when other direct and indirect non-drugs costs (such as physician visits, hospitalisation, adverse events, productivity losses) associated with aciclovir would be substantially greater than those with valaciclovir. Based on the clinical trial evidence provided, this is unlikely to be the case.

The Committee also noted that there are no published studies of the cost-effectiveness of valaciclovir or aciclovir in the treatment of herpes simplex in HIV infected patients. One published trial comparing the cost-effectiveness of valaciclovir and aciclovir in the treatment of herpes simplex virus (Grant et al., 1997) reported that valaciclovir reduced direct medical costs by an average of 17% (US$ 60.01) and indirect medical costs by an average of 25% (US$ 46.54) compared to aciclovir. However, the published analysis is actually a cost-consequence

analysis rather than a true cost-effectiveness analysis. As this analysis was highly system specific the Committee did not consider it necessarily applicable to other settings.

The Committee concluded that valaciclovir could only be considered cost-effective if its price were reduced sufficiently, or if evidence were to be presented that adherence to treatment and treatment outcomes are considerably better than with aciclovir. In the absence of such information the Committee recommended that valaciclovir should not be added to the list, but that aciclovir should become a 'boxed' drug for this indication with valaciclovir mentioned as one of the alternatives in the same pharmacological class.

Applications for deletion

ethinylestradiol + levonorgestrel tablet, 50 microgram + 250 microgram (pack of four)

A request was received from the WHO Department of Reproductive Health and Research to delete from the Model List ethinylestradiol + levonorgestrel tablet, 50 microgram + 250 microgram (pack of four). The Committee was informed that, compared to the combined regimen of ethinylestradiol and levonorgestrel (four-pill pack), a levonorgestrel-only regimen is associated with significantly less side-effects[9][10] and was also more effective in a large randomized double-blind multinational study organized by the Special Programme of Research, Development and Research Training in Human Reproduction at WHO[11]. Since this publication in 1998, the levonorgestrel-only regimen has been registered in over 90 countries and some manufacturers have taken the four-pill pack off the market. More recently, a randomized, double-blind trial demonstrated that one dose of 1.5 mg levonorgestrel has the same efficacy without increasing side-effects as the two doses of 0.75 mg of levonorgestrel at 12-hour interval[12]. Therefore one dose of 1.5 mg of levonorgestrel is now recommended for emergency contraception. Currently the packs contain two tablets of 0.75 mg but it is likely that in the future there will also be single tablets of 1.5 mg available for this indication.

The Committee noted that there are two dosage forms for emergency contraception on the 12th WHO Essential Medicines List of 2002: ethinylestradiol + levonorgestrel tablet, 50 micrograms + 250 micrograms (pack of four) and, levonorgestrel tablets, 750 micrograms (pack of two). The application for deletion of the combination 4 tablet pack is supported by the high level of clinical evidence of its inferiority to the levonorgestrel only regimen in the Cochrane Systematic Review. The Committee also noted that the better safety profile of the levonorgestrel only regimen was confirmed by statistically and clinically significant fewer side effects with the resulting RR: 0.80, 95% CI: 0.74 to 0.86. Nausea (16.1% *vs* 46.5% and 23.1% *vs* 50.5%) and vomiting (2.7% *vs* 22.4% and 5,6% *vs* 18.8%) occurred less frequently with levonorgestrel regimen (P<0.01). The latest WHO multicentre (15 family-planning clinics in 10 countries,

[9] Ho PC, Kwan MSW. A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. *Hum Reprod* 1993; 8:389-92 .
[10] Cheng L et al. Interventions for emergency contraception. In the Cochrane Library, Issue 1, 2003. Oxford: Update Software.
[11] Task Force on Post-ovulatory Methods of Fertility Regulation. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998; 352:428-33.
[12] Helena von Hertzen et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomized trial. *Lancet* 2002; 360: 1803

4,071 women participants) randomized trial of two regimens of levonorgestrel for emergency contraception (single-dose 1.5 mg and two-dose 0.75 mg 12 hours apart) demonstrated high and equal efficacy of both regimens if taken within five days of unprotected coitus. The pregnancy rates were 1.5% (20/1356) in women assigned single dose levonorgestrel and 1.8% (24/1356) in those assigned two-dose levonorgestrel (no statistical difference, p=0.83). The relative risk of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0.83 with 95% CI 0.46-1.50.

The Committee concluded that there was good evidence that a 1.5 mg single levonorgestrel dose can substitute the two-dose regimen (0.75 mg 12 hours apart) and that the use of a single dose simplifies the use of levonorgestrel for emergency contraception without an increase in side effects. The Committee therefore recommended that the 1.5mg tablet be added as a new dosage form of levonorgestrel and that ethinylestradiol + levonorgestrel tablet, 50 micrograms + 250 micrograms (pack of four) be deleted from the list.

Nonoxynol

A request was received from the WHO Department of Reproductive Health and Research to delete nonoxynol as a condom-additive vaginal spermaticide and virucidal. In addition, a summary analysis of safety was received from the WHO Collaborating Centre for International Drug Monitoring in Uppsala, and a copy of the (US)FDA proposed rule on the labelling of over-the-counter vaginal contraceptive drug products containing Nonoxynol-9.

In the application reference was made to a large multicountry study sponsored by WHO/GPA and UNAIDS published in *The Lancet* in September 2002.[13] Contrary to expectation the study showed that women using nonoxynol-9 had a higher incidence of HIV infection than women using the placebo gel. Prompted by these data, the WHO Department of Reproductive Health and Research, in partnership with the CONRAD Program, convened a Technical Consultation in October 2001 to review the implications of these new data on the use of nonoxynol-9 as a spermicide.[14] All evidence regarding the use of nonoxynol-9 as a contraceptive, its effectiveness in preventing infection with gonorrhoea or *Chlamydia trachomatis*, and its effectiveness in preventing HIV infection available at the meeting is summarised in the report. Key conclusions from the consultation include:

- Although nonoxynol-9 has been shown to increase the risk of HIV infection when used frequently by women at high risk of infection, it remains a contraceptive option for women at low risk.
- Nonoxynol-9 offers no protection against sexually transmitted infections such as gonorrhoea or Chlamydia.
- There is no evidence that condoms lubricated with nonoxynol-9 are any more effective in preventing pregnancy or infection than condoms lubricated with silicone, and such condoms should no longer be promoted. However, it is better to use an nonoxynol-9 lubricated condom than no condom at all.
- Nonoxynol-9 should not be used rectally.

Subsequent to the Consultation, the final paper from the COL-1492 study and the systematic review of nonoxynol-9 for STI and HIV prevention[15] have been published. In the light of the above evidence the RHR Department recommended that the specific mention of condoms

[13] Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-transmission among female sex workers. *Lancet* 2002;**360**:971-977.
[14] http://www.who.int/reproductive-health/rtis/ N9_meeting_report.pdf
[15] Wilkinson D, Tholandi M, Ramjee G, Rutherford GW. Nonoxynol-9 spermicide for prevention of vaginally acquired HIV and other sexually transmitted infections: systematic review and meta-analysis of

lubricated with nonoxynol-9 should be removed from the Model List, but that condoms must be retained on the Model List. They are well proven to prevent pregnancy as well as HIV and STI transmission, and are the mainstay of HIV and STI prevention programs. Silicone-oil lubricant is recommended in the WHO Technical Specifications for Male Latex Condoms.

On the basis of the evidence presented the Committee recommended to maintain condoms on the Model List but to delete the mention to nonoxinol-9 in view of the increased risk of transmitting HIV infection[16]. As there is insufficient evidence to suggest an alternative spermicide, the Committee recommended to delete the reference to spermicides as well.

With regard to diaphragms, the Committee noted its continued need as part of the contraceptive mix offered for family planning, despite its moderate contraceptive effect. For this reason the Committee recommended that the diaphragm be maintained on the list.

With regard to the use of nonoxinol-9 with a diaphragm the Committee noted that most observational studies are done with spermicide and that one randomized study found a statistically non-significant additional beneficial effect of the spermicide in preventing pregnancy.[17] The Committee therefore recommended to remove the reference to spermicides, including nonoxinol, in view of the lack of evidence of benefit and the strong suggestion of potential to increase risk of transmission of HIV infection.

randomized controlled trials including more than 5000 women. *Lancet Infectious Diseases* 2002;**2**:613-617.

[16] Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-transmission among female sex workers. *Lancet* 2002;**360**:971-977.

[17] Bounds W, Guillebaud J, Dominik R, Dalberth BT. The diaphragm with and without spermicide. A randomized, comparative efficacy trial. J Reprod. Med 1995; 40: 764-74

Application for addition of information

Anti-leprosy medicines

The Committee reviewed a request received from the WHO Department of Communicable Diseases Prevention, Control and Eradication to modify the text in the Model List in order to better reflect the fact that anti-leprosy medicines should be used exclusively in combination (as Multidrug Therapy, MDT) and presented in colour coded blister packs (MDT blister packs) in order to (1) prevent antimicrobial resistance, (2) improve patient adherence to treatment and (3) facilitate logistics and inventory control; and that MDT blister packs can be obtained free of charge through WHO.

The Committee recommended the existing text in the Model List be replaced with the following text at the head of the section:

> *Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour coded blister packs (MDT blister packs) containing standard two medicine (paucibacillary leprosy) or three medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.*

The committee also recommended that the same information be included in the WHO Essential Medicines Library and the WHO Model Formulary.

Applications for change

Oral Rehydration Salts (change in formula)

The Committee reviewed an application by the Department of Child and Adolescent Health to change to formula of Oral Rehydration Salts. The current formula, which provides a solution containing 90 mEq/l of sodium with an osmolarity of 311 mOsm/l has proven effective and without apparent adverse effects in world wide use and has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease.

The Committee was informed that, for the past 20 years, numerous studies have been undertaken to develop an "improved" ORS. The goal was a product that would be at least as safe and effective as standard ORS for preventing or treating dehydration from all types of diarrhoea but which, in addition, would reduce stool frequency or have other important clinical benefits. One approach has been to reduce the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. This was done by reducing the solution's glucose and salt (NaCl) concentrations .

Studies to evaluate this approach were reviewed at a consultative technical meeting in New York in July 2001, and technical recommendations were made to WHO and UNICEF on the efficacy and safety of reduced-osmolarity ORS in children with acute non-cholera diarrhoea, and in adults and children with cholera. These studies showed that the efficacy of ORS solution for treatment of children with acute non-cholera diarrhoea is improved by reducing the sodium concentration to 75 mEq/l, the glucose concentration to 75 mmol/l, and the total osmolarity to 245 mOsm/l. Compared to established ORS, the need for unscheduled supplemental intravenous therapy in children given the reduced-osmolarity ORS was reduced by 33% (NNT 20). In a combined analysis of this study and studies with other reduced-osmolarity ORS solutions (osmolarity 210-268 mOsm/l, sodium 50-75 mEq/l) stool output was also reduced by about 20% and the incidence of vomiting by about 30% [18]. The 245 mOsm/l solution also appeared to be as safe and at least as effective as standard ORS for use in children with cholera.

The application also mentioned that the reduced-osmolarity ORS containing 75 mEq/l sodium, 75 mmol/l glucose (total osmolarity of 245 mOsm/l) is as effective as standard ORS in adults

[18] Reduced osmolarity oral rehydration salts (ORS) formulation – Report from a meeting of experts jointly organized by UNICEF and WHO. WHO/CAH/01.22
http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/Expert_consultation.htm

with cholera. However, it is associated with an increased incidence of transient, asymptomatic hyponatraemia. This reduced-osmolarity ORS may be used in place of standard ORS for treating adults with cholera, but careful monitoring is advised for significant hyponatraemia.

The Committee noted that the new ORS formulation was already officially released by WHO and partners during the United Nations General Assembly Special Session on Children in New York; and that UNICEF, USAID and MSF are supporting this application.

In its discussions the Committee noted that WHO and UNICEF have published criteria for acceptable ORS formulations. These criteria are listed below; they specify the desired characteristics of the solution after it has been prepared according to the instructions on the packet:

The total substance concentration	(including that contributed by glucose) should be within the range of **200-310 mmol/l**
The individual substance concentration	
Glucose	Should at least equal that of sodium but **should not exceed 111 mmol/l**
Sodium	Should be within the range of **60-90 mEq/l**
Potassium	Should be within the range of **15-25 mEq/l**
Citrate	Should be within the range of **8-12 mmol/l**
Chloride	Should be within the range of **50-80 mEq/l**

The Committee concluded that the evidence for the benefits of the new formula for acute non-cholera diarrhoea in children was convincing, with a 5% absolute risk reduction (NNT = 20) in the need for unplanned IV infusions, and recommended that the formula be changed to 75 mEq/l sodium (sodium chloride 2.6 g/liter) and 75 mmol/l (13.5 g/liter) glucose. The Committee also recommended that the following footnote be added: *In cases of cholera a higher concentration of sodium may be required.*[19]

[19] Reduced osmolarity oral rehydration salts (ORS) formulation. Consensus statement of WHO and UNICEF. Geneva: World Health Organization; 2001. Document WHO/FCH/CAH/01.22

Streptokinase (dosage modification)

The Committee reviewed the application received from Aventis Behring to remove the 100,000 IU dosage from the list.[20] The Committee noted that the standard dosage in the main indication, treatment of acute myocardial infarction, is 1.5 Million IU. The Committee recommended that the dosage be changed to powder for injection 1.5 million IU in vial. The note (for use in rare or exceptional circumstances) should be removed since its value in treating acute myocardial infarction has been demonstrated and its use is no longer reserved for exceptional situations.

[20] The full application and the comments are posted on the EDM web site and in the Essential Medicines Library.

Fast-track procedure for deletion

In 2002 the Expert Committee recommended that, for certain items on the Model List, a fast-track procedure for deletion should be used. The background to this recommendation was that certain items on the Model List could be considered as obsolete for which no systematic reviews or sufficient evidence of efficacy and safety were available; but that the fact that they were probably obsolete or not essential did not justify the costly investment of a full systematic review.

A consultation technique was used to identify those medicines most in need of review or fast-track deletion. In addition, the review of the square box symbol and the review of the core/complementary listing led to several recommendations for review or fast-track deletion; the recommendations were reviewed by peers, and finally by the WHO Secretariat.

A questionnaire was used to identify those medicines on the WHO Model List of Essential Medicines (EML) which either required review on the basis of doubtful safety and/or efficacy, or which could be proposed for fast-track deletion. A small group of international experts was formed from the 2002 Expert Committee on the Selection and Use of Essential Medicines, and the Secretariat. The work was carried out in two main areas. One questionnaire comprised a list of drugs that were compiled from a number of sources. Some were considered by the wider committee to be questionable in terms of safety and/or efficacy, some were identified by a survey identifying which medicines listed on the model list also appeared on a sample of 12 national lists, and others were identified by the Secretariat. The second questionnaire was a simple list of the pharmacological section headings used in the Model List with a request to rank those sections considered to be in need of revision.

The first questionnaire was sent to 81 individuals provided by the Secretariat, consisting of Expert Panel members, members of a wider advisory group and relevant WHO staff including regional advisers. In addition a message was posted on the e-drug electronic discussion group, which resulted in another 27 expressions of interest. In return to 104 forms sent out, 28 (24%) completed forms were received from 20 countries.

On the basis of the outcome of the questionnaire[21] the Committee recommended to retain the following three medicines on the Model List: codeine for analgesic use, pyrantel and verapamil tablets.

The Committee also recommended, on the basis of the outcome of the questionnaire and other arguments as mentioned below, to delete or change the following medicines from the Model List.

Chloral hydrate

The Committee noted that it was only included on 2 out of 25 national essential drugs lists. It also noted that chloral hydrate was mentioned in the 1998 WHO publication on Cancer Pain Relief as "drug of choice for painless procedures" but concluded that there were many effective and safe alternatives, such as promethazine syrup; and recommended that it be deleted from the list.

Clomifene

The Committee noted that subfertility is common and can cause considerable distress, that there is a Cochrane review[22] showing its effectiveness (NNT 2.74) but no WHO clinical guidelines on infertility, and that it is listed on 20 of 25 national essential medicines lists. The Committee recommended to maintain clomifene on the list but move it to the complementary list in view of the need for specialist care and to remove the square box symbol.

Dextromethorphan, oral solution

The Committee noted the conclusion of the WHO clinical guideline[23] which reads "Given the conflicting nature of the evidence, no clear recommendation can be made in favor of its use" and the outcome a recent Cochrane review[24] which showed no good evidence for OTC medications against cough. The Committee concluded that there was insufficient evidence to list it as an essential medicine and recommended that the item be deleted.

Fludrocortisone

[21] The first number indicates the number of votes to delete the item, the second the votes to maintain it.
[22] Hughes et al. Clomiphene citrate for ovulation induction in women with oligo-amenorrhoea. In: The Cochrane Library, issue 1, 2003. Oxford, Update Software
[23] Cold and cough remedies for the treatment of acute respiratory infections in young children. Geneva: WHO, 2001. Document WHO/FCH/CAH/01.02
[24] Schroeder H, Fahey T. Over the counter medications for acute cough in children and adults. In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software

The Committee noted that this is a life-saving drug in adrenal insufficiency, which is considered a rare condition, that it figures in 9 of 25 essential medicines lists, that it is not listed in the MSH drug price indicator and not being supplied by UNICEF and IDA. The Committee concluded that there is no need for this item on the list and recommended that it be deleted.

Folic acid injection

The Committee noted that there was no identified need for this presentation; and recommended that it be deleted from the list.

Immunoglobulin human normal

The Committee noted that there is no need for this medicine in view of the availability of relevant vaccines, that there are no WHO clinical guidelines recommending its use, and that quality control of this blood product poses a problem. The Committee recommended to delete this item from the list.

Ipecacuanha

The Committee noted the lack of need for an emetic in the treatment of poisoning due to risk of aspiration pneumonia, and the lack of evidence on efficacy and safety of ipecacuanha in the management of poisoning; it also noted that ipecacuanha was not included in the Chemical Safety IPCS-INTOX databank and recommended that it be deleted from the list.

The Committee noted that special drugs, such as fludrocortisone and antihaemophilia globulin were deleted from the list because, on reflection, the Committee considered the diseases for which they are needed are too uncommon for these items to "satisfy the priority health care needs of the population". The Committee fully recognized the essential and even life saving nature of certain drugs for patients with rare but treatable diseases. While the treatment for such diseases, on reflection, fall outside the charge of the Committee, the Committee urged that effective treatments for serious uncommon diseases be made available to these patients whenever possible. At the national level, special arrangements for specific individuals may need to be made in this regard.

In view of the other outcomes of the questionnaire the Committee recommended that the sections on anaesthetics and dermatological medicines be reviewed systematically before any further deletions could be recommended in these groups. For a systematic review of section 12.3, see page ????.

Review of Core and Complementary Listing

The 2002 Model List of Essential Medicines is presented in two sections: a 'core' list, and a 'complementary' list, printed separately. The 2002 descriptions of each are as follows:

*The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost effective medicine for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.*

*The **complementary list** presents essential medicines for priority diseases which are efficacious, safe and cost-effective but not necessarily affordable, or for which specialised health care facilities or services may be needed.*

At the meeting of the Committee in 2002 there was considerable discussion about whether the system of two lists should be retained or whether they should be combined into a single list. This suggestion was prompted in part by the observation that the criteria for a 'core' or 'complementary' had become blurred; and had also been misapplied to drugs that were for priority conditions but were thought to be expensive. As the prices of pharmaceuticals are variable and changing, it did not seem reasonable to use 'cost-effective but not necessarily affordable' as the main criteria for inclusion of a product on the complementary list.

Following this discussion, in the course of 2002 all medicines on both lists were reviewed on the basis of the following general principles:

1. All essential medicines are on the 'core' list, unless there is a specific reason for them to be on the complementary list
2. If there is uncertainty about the classification, the medicine will be put on the core list

The following criteria were used for putting a drug on the complementary list:

1. Primary criterion: Use of the medicine requires specialised diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training
2. Secondary criterion, only used in case of doubt: Consistent higher cost or less attractive cost-effectiveness in a variety of settings.

On the 2002 Model List, 79/325 (24%) medicines are listed as complementary; some are listed on both lists. For each medicine the indications and specifications for use described in the WHO

Model Formulary were reviewed. Where the formulary indicates that there is always a need for specialist medical care or facilities for use of a medicine, it was classified as complementary. Where there was uncertainty, consistent higher cost or less attractive cost-effectiveness in most settings was used as a secondary criterion. When still in doubt, the medicine was classified as core.

The Committee decided to define the criteria for core and complementary lists, as follows:

> *The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost effective medicine for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.*
>
> *The **complementary list** presents essential medicines for priority diseases, for which specialised diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.*

The Committee recommended that the two lists be combined as one, with medicines on the complementary list printed in italics or otherwise identified.

The Committee then reviewed the proposals for the two lists. In doing so it decided not to make recommendations for changes in sections which were also recommended for systematic review; such changes were to be recommended as part of such reviews.

The Committee recommended that the following medicines be moved from the core list to the complementary list: azathioprine, clomifene, diethylcarbamazine, dopamine, ethosuximide, hydrocortisone rectal preparations, intraperitoneal dialysis solution, methotrexate, penicillamine, pentamidine, pyridostigmine, sulfadiazine and sulfasalazine.

The Committee recommended that the following medicines be moved from the complementary list to the core list: amoxicillin/clavulanic acid, chloramphenicol oily solution, epinephrine (adrenaline) injection, levonorgestrel, mannitol and norethisterone enantate.

The Committee recommended that the following items be deleted from the list:

Cyclophosphamide as disease-modifying agent in rheumatoid arthritis

The Committee noted a Cochrane review[25] on the efficacy and safety of cyclophosphamide as a disease-modifying agent in rheumatoid arthritis, and recommended that this item be deleted for this indication.

Desmopressin (due to rarity of the indication).

Iron dextran injection (due to unfavourable benefit/risk ratio)

Pethidine

The Committee noted that pethidine was listed on 19 of national 25 lists studied; but that pethidine was considered inferior to morphine due to its toxicity on the central nervous system; and that it is generally more expensive than morphine. The Committee concluded that there was insufficient justification to keep pethidine on the list and recommended that it be deleted. The Committee also stressed that all national programmes should ensure that sufficient quantities of morphine are always available for those who need it.

[25] (Check authors and title) In: The Cochrane Library, issue 1, 2003. Oxford, Update Software

Review of use of Square Box Symbol

In the 2002 Model List 113 medicines are marked with a 'square box' symbol. The statement in the preamble to the 2002 Model List regarding the use of a 'square box' is:

> "*The **square box** symbol indicates that a listed medicine should be seen as a representative example from a group of clinically equivalent medicines with wide experience of use, within a pharmacological class. The medicines listed on the Model List would generally be the least costly therapeutic equivalent within the group. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.*"

In the Expert Committee meeting in 2002 it was considered that there was some confusion and inconsistency about the way this symbol has been used. For example, neostigmine is listed with a square box yet there is no pharmacological or therapeutic equivalent; several different corticosteroids are on the list and some are marked with boxes for some purposes while others are not.

Following this discussion, the Committee reviewed all uses of the square box symbol. In doing so, it was first necessary to redefine the meaning of the square box symbol. When considering medicines, there are three possible ways of defining 'equivalence' and 'interchangeability'.

The first definition is based on *generic* equivalence, where products contain the same chemical compound. In this regard, the Committee recommended to use the existing description[26] which reads: "*The term "generic product" has somewhat different meanings in different jurisdictions and in this document use of the term is avoided as much as possible, and the term "multisource pharmaceutical product" has been applied. Generic products may be marketed either under the nonproprietary approved name or under a new brand (proprietary) name. They may sometimes be marketed in dosage forms and/or strengths different from those of the innovator products. However, where the term "generic product" has to be used it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of patent or other exclusivity rights.*" Generic substitution is assumed to be acceptable for the Model List as the list is constructed by chemical compound, not brand. The Committee recommended that

[26] Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for drug regulatory authorities. Geneva, WHO, document ... Annex 3, page 109

square boxes should not be used to indicate substances for which there are known to be multiple suppliers of acceptable products.

The second level of interchangeability is at the level of pharmacological class, e.g. ACE inhibitors. There are a number of papers describing the debate about 'class effects' of medicines and whether efficacy and safety can be assumed to be interchangeable throughout a class of drugs. It is fair to say that the debate has not been concluded. There is some evidence that efficacy can be assumed across a class of drugs if equipotent doses of the drugs can be established, but that safety can not necessarily be generalised in the same way. From a policy point of view, it can be useful to define pharmacological items within a class that are deemed to be clinically similar on the basis of the best comparative evidence, and then to set medicine reimbursement levels accordingly.

The Committee agreed that for the Model List the 'square box' symbol should be used primarily to indicate similar clinical performance within a pharmacological class.
The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.

The third possible definition of interchangeability is based on therapeutic indication. Determining therapeutic equivalence is complex. An example would be to suggest that all classes of drugs used to treat hypertension are therapeutically interchangeable, a suggestion that has been hotly debated. Defining 'therapeutic groups' of medicines for specific indications requires comprehensive reviews of the clinical data on comparative effectiveness and safety, and can be the subject of considerable controversy.

The Committee agreed to use the square box symbol on the basis of the following description:

> *"The square box symbol is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms*

of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price."

In doing the review the following principles were used:
1) Items on the Model List should primarily be listed without the square box symbol; the symbol should only be used if there are at least one other member of its pharmacological class which can be considered as clinically similar; and such item(s) should be identified and listed as examples in the Essential Medicines Library and/or the Model Formulary.
2) For any item for which there is uncertainty about the clinical similarity of any potential alternatives, no symbol should be used.

Based on this review the Committee recommended that the following square box symbols be removed from the following items: amiloride, amoxicillin, amoxicillin/clavulinic acid, antitetanus immunoglobulin, azathioprine, chloramphenicol, chloroquine, ciclosporin, clomifene, charcoal activated, codeine, cycloserine, dexamethasone, diloxanide, DL-methionine, doxorubicin, doxycycline, epinephrine/adrenaline, ethionamide, hydrocortisone, glibenclamide, ibuprofen, mannitol, morphine, promethazine, quinine, sodium nitroprusside, retinol, sulfadiazine, sulfadoxine/pyrimethamine, sulfamethoxazole/trimethoprim and verapamil.

In making these recommendations the Committee noted the following:
The square box for ibuprofen was removed because there are significant differences in efficacy and safety within this pharmacological class. The square box for morphine was removed because of the lower benefit/risk ration and higher price of alternatives; the Committee urged all national programmes to ensure that sufficient quantities of morphine are always available to those who need it.

In the following cases the Committee recommended that the square box symbol be retained but the listed medicine be changed: cloxacillin to be replaced by dicloxacillin (being the most active in its class, available as a generic), captopril to be replaced by enalapril (because of simpler dosing regimen, available as a generic) and cimetidine to be replaced by ranitidine (because of

simpler dosing regimen and less potential for pharmacokinetic interactions, available as a generic).

The Committee recommended that examples of possible alternatives for the medicines with a square box should not be included in the report or in the Model List, but be mentioned in the Essential Medicines Library and the Model Formulary.

Corticosteroids

The Committee reviewed the corticosteroids included on the list and noted that there is very limited systematic evidence to compare the various corticosteroids in human use, and on the relationship between dose and effect in various conditions. The Committee noted that the list is not very consistent in its recommendations on the selection of corticosteroids and the use of the square box symbol, and recommended that the listing of corticosteroids for systemic use be simplified as follows.

On the core list, in section 3 (antiallergics and anaphylactic shock), prednisolone tablets 5mg and 25mg should be the only oral preparation with a square box, in view of its slightly lower price per DDD and considerably higher turnover by not-for-profit generic suppliers when compared to dexamethasone 500 micrograms. The Committee recommended that dexamethasone be mentioned as the possible alternative, and that the following footnote be added: " *There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses*". The Committee also recommended that dexamethasone, injection 4mg dexamethasone phosphate (as disodium salt) in 1ml ampoule, and hydrocortisone, powder for injection, 100mg (as sodium succinate) in vial should both be listed as injectable corticosteroids, without square box symbol.

On the complementary list, in section 8.3, the same items should be listed with the same footnote.

In section 18.1 (core and complementary list) all corticosteroids should be deleted in view of the rarity of the condition; however, the section heading in the list should be maintained with the following text: *Addison's disease is a rare condition; adrenal hormones are already included in section 3.*

The Committee recommended that betamethasone 0.1% and hydrocortisone 1% cream or ointment in section 13 and prednisolone eye drops 0.5% (sodium phosphate) in section 21 be kept on the list, pending a full review of these sections. The Committee also recommended that hydrocortisone suppository 25mg (acetate) and retention enema be kept on the list.

Review of section 12.3 Antihypertensive medicines

The Committee was informed by the Department of Cardiovascular Diseases that WHO plans to incorporate the revised WHO/International Society of Hypertension guideline of 2002 into a Cardiovascular Risk Assessment and Management guideline, so as to bring about a paradigm shift from single risk factor management to comprehensive cardiovascular risk management. It is envisaged that this work will be completed by the end of 2003. In the interim, it has been agreed that a statement be made on the management of hypertension by the group of experts assigned to update the WHO/ISH Hypertension Guidelines of 1999, reflecting their evidence-based work. This statement will supersede the WHO/ISH Guidelines 1999 and will be made available on the internet in the spring of 2003.

The Committee compared the antihypertensive medicines currently listed in section 12.3 with the draft statement from WHO. The statement proposes that, on the basis of the current evidence, first line drug treatment of hypertension should be thiazide diuretics, β-blockers or ACE-inhibitors. The role of calcium channel blockers is less certain; it is suggested that they should be used as first-line treatment in some populations (e.g. the elderly, based on their benefits in terms of stroke (from the SHEP trial) or in African Americans (Veterans Affairs study, published 2000)) but that their place as a first line agent for other populations is less clear.

The Committee noted that the role of the older drugs (reserpine, hydralazine and methyldopa) is now questionable. Systematic reviews of the trials of each drug have been carried out and have been published or submitted for publication in the Cochrane database (Manyeba et al, Pillay and O'Reagan). On the basis of these reviews, it appears that there are few large randomized trials that report clinical outcomes (mortality, stroke, AMI) for these medicines, that there are no large comparative clinical trials that report comparative efficacy and safety, and that there are significant side effects from all of these medicines. In addition, following the publication of the ALLHAT trial in December 2002, the role of α-blockers in the treatment of hypertension should also be questioned. In that study, patients treated with doxazosin had higher mortality rates than those in other treatment groups (chlorthalidone, amlodipine and lisinopril) and the doxazosin arm of the study was suspended early. With regard to the other treatment groups in that study, there was no significant difference between chlorthalidone, amlodipine and lisinopril treatment for the primary outcome of the study, development of coronary heart disease.

The Committee also noted that hydralazine, reserpine and methyldopa are all off-patent and usually relatively cheap. However, this alone is no justification to keep them on the Model List as some of the ACE inhibitors and calcium channel blockers are now also off-patent, and are probably safer and more effective.

On the basis of the current evidence the Committee recommended that reserpine and hydralazine be deleted from the list on the basis of lack of evidence of long-term effects on mortality and morbidity and the availability of better and safer alternatives. The Committee recommended that prazosin be deleted as a complementary drug, in view of the lack of evidence for additional benefit and given that adverse effects of doxazosin on mortality and morbidity may be a class effect. The Committee recommended that captopril be replaced by enalapril as the listed example of the therapeutic group, on the basis of an easier dosage schedule.

In relation to the use of calcium channel blockers, preliminary evidence was presented to the Committee that suggested that dihydropyridine calcium channel blockers as a class should not be used as first line treatment for hypertension, because of the potential increased risk of adverse outcomes. The Committee recommended that there should be a thorough and critical review of the justification of the use of dihydropyridine calcium channel blockers as first-line treatment for hypertension for the next meeting and that a decision would then be made about their retention or deletion from the list.

The Committee considered the question of the appropriate treatment of pregnancy induced hypertension (PIH) which is not considered in the WHO draft Statement. There have been two published Cochrane reviews on the topic, one in mild-moderate PIH (last updated in 2000) and one in severe PIH (updated 2002). The first review concluded that the data were not sufficient to determine whether drug treatment was worthwhile at all; the second that treatment should be with a drug with which the physician was familiar. Subsequent studies have suggested that in term of effects on the child, methyldopa is the drug of choice as it appears to have least impact on long term development.

The Committee recommended that methyldopa be kept on the core list but that the following note should be added: "*Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.*" The Committee acknowledged that there is only limited evidence for this recommendation regarding the use of methyldopa in pregnancy, but that methyldopa seems to be the safest alternative for the fetus.

The Committee recommended that more research be done on the treatment of hypertension in pregnancy specifically addressing long-term outcomes and child development.

The Committee reviewed a proposal from the Secretariat to add magnesium sulphate as antihypertensive on the complementary list, specifically for treatment of pre-eclampsia. The Committee noted that pre-eclampsia is estimated to complicate 2-8% of pregnancies. The disorder is usually associated with raised blood pressure and is a major cause of morbidity and mortality for the woman and her child. Anticonvulsant drugs have been used in women with pre-eclampsia in the belief that they reduce the risks of seizure. Following a systematic review of existing trials of treatment, magnesium sulphate was identified as the most promising agent to investigate in a large trial. The MAGnesium sulphate for Prevention of Eclampsia (MAGPIE) trial covered 10141 women in 33 countries and was published in June 2002. The conclusion from the trial is that magnesium sulphate halves the risk of eclampsia and probably reduces the risk of maternal death.

The Committee noted that magnesium sulfate is already listed on the core list, in section 5: anticonvulsants/antiepileptics and decided to add a note that this medicine is for use in eclampsia and severe pre-eclampsia and not for other convulsant disorders. The Committee urged that this drug be made more generally available in view of the strong evidence demonstrating its benefit.

In summary, the Committee recommended that the following medicines be listed in section 12.3:

12.3 antihypertensives (core list)

Boxed **atenolol** tablet 50mg, 100mg

Boxed **enalapril** tablet 25mg

Boxed **hydrochlorothiazid**e scored tablet 25mg

Methyldopa tablet 250mg (with note: for use in pregnancy-induced hypertension only

Boxed **nifedipine** (with note)

Complementary list

Sodium nitroprusside, powder for infusion, 50mg in ampoule (box removed)

Priorities for review

Sections recommended for review, with level of priority

1.2 Anaesthetics (high priority; include muscle relaxants, premedication, ephedrine)

2.4 Disease modifying agents used in rheumatoid disorders (DMARDS)
3 Antiallergics (low priority)
6.2.1 Cephalosporins (high priority)
6.3 Antifungals (high priority)
7.2 Migraine (low priority)
8 Oncology (high priority)
11.1 Plasma expanders (high priority)
11.2 Plasma fractions (high priority)
12.2 Antiarrhythmics (high priority)
13 Dermatology (medium priority)
14 Diagnostic agents (medium priority)
15 Disinfectants (low priority)
17.6 Laxatives (low priority)
20 Muscle relaxants (with anaesthetics)
21 Ophthalmological preparations (high priority)
25 Antiasthmatics (high priority)
26 Intravenous solutions (medium priority)

The Committee also recommended that a special review be carried on the use of medicines in paediatrics.

Review for possible deletion at next meeting
1.1 ether (review actual consumption)
2.2 codeine
2.3 colchicine
5.0 clonazepam
6.1.1 niclosamide
6.1.1 pyrantel,
6.1.3 triclabendazole
6.1.3 oxamniquine
6.2.1 imipenem/cilastatin
6.2.2 nalidixic acid
6.2.2 spectinomycin
6.2.4 levofloxacin
6.2.4 thioacetazone/isoniazid
6.6 diethyltoluamide

7.1 ergotamine

11.1 polygeline

11.2 Factor IX and factor VIII

12.2 isoprenaline

12.2 procainamide

12.2 quinidine

12.3 nifedepine

13.7 topical sun protection agent

17.3 local anaesthetic/astringent ointment

17.5 atropine

18.3.1 (and 18.7) medroxyprogesteron acetate

21.1 silver nitrate eye solution

22.1 ergometrine

22.2 salbutamol

25.1 aminophylline

25.1 cromoglicic acid

25.1 theophylline

27 calcium gluconate

27 sodium fluoride

The Committee recommended that these items be marked in the list with the following footnote: *"The efficacy and safety of this item or group has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee".*

Review of activities to promote rational drug use

Update on activities to contain antimicrobial resistance

Antimicrobial resistance refers to strains of micro-organism that are able to multiply in the presence of antimicrobial drug concentrations higher than in the concentrations in humans receiving therapeutic doses. The development of resistance is a natural biological phenomenon that has followed the introduction of every antimicrobial agent into clinical practice. Increased antimicrobial use is associated with increased rates of resistance and, hence, irrational overuse of antimicrobials is contributing to the increasing global problem of antimicrobial resistance. Antimicrobials are over-used world-wide at all levels of the health care system in amounts that are perhaps double what would be clinically indicated. Resistance rates vary locally depending upon local antimicrobial use.

The World Health Assembly has recognised antimicrobial resistance as a serious public health problem. The World Health Assembly Resolution of 1998 urged member states to develop measures to encourage appropriate and cost-effective use of antimicrobials. However the problem of resistance including multi-drug resistance has continued to grow while the development of new antimicrobials is decreasing. The WHO global strategy (WHO 2001) addresses this challenge by providing a framework of interventions to slow the emergence and reduce the spread of antimicrobial resistant micro-organisms. More than 60 interventions were chosen and prioritised on the basis of invited expert opinion with wide review. It was agreed that an adequately funded multi-sectoral task force and reference laboratory, to conduct jointly surveillance of antimicrobial resistance and use, were fundamental to any national containment programme.

The interventions deemed most important were:

- Patient education on preventing infection (immunization, bednets) and reducing transmission (hand washing, food hygiene)
- Provider education on antimicrobial use, AMR containment, disease prevention, infection control
- Targeted undergraduate and postgraduate education for all health workers and veterinary practitioners on accurate diagnosis and management of common infections
- Development, updating and use of clinical guidelines and treatment algorithms
- Infection Control Programmes in hospitals
- Good quality diagnostic laboratories
- Limitation of availability of antimicrobials to prescription-only

- Granting marketing authorisation only to antimicrobials which meet international standards of quality, safety and efficacy

Very few countries have a national antimicrobial resistance containment programme. Reduction of antimicrobial resistance has been observed in a few countries that have succeeded in significantly reducing antimicrobial consumption and improving infection control. Many countries do not base their choice of antimicrobials for an essential medicines list or standard treatment guidelines on epidemiologically sound antimicrobial resistance data even though this is crucial for ensuring best patient outcome and use of antimicrobials. Containing antimicrobial resistance and ensuring that patients are treated with the most effective antimicrobials requires the linked surveillance of antimicrobial resistance and consumption. WHO is now supporting pilot projects to develop a feasible new model and methodology for such linked surveillance of antimicrobial resistance and consumption and the local containment of antimicrobial resistance in developing countries. However, much more political and financial commitments would be needed in the future.

Guidelines for Drugs and Therapeutic Committees

A drugs and therapeutics committee (DTC), also called a pharmacy and therapeutics committee, is designated to ensure the safe and effective use of medicines in the facility or area under its jurisdiction. Such committees are well-established in industrialized countries as a successful way of promoting more rational, cost-effective use of medicines in hospitals. WHO is promoting DTCs through international training courses run in collaboration with Management Sciences for Health, the development and publication of a manual on DTCs, and research projects.

The main responsibilities of a DTC consist of:

- Developing, adapting, or adopting clinical guidelines for the health institution or health facilities under its jurisdiction;
- Selecting cost-effective and safe medicines (hospital/health facilities' drug formulary);
- Implementing and evaluating strategies to improve medicine use (including drug use evaluation, and liaison with antibiotic and infection control committees);
- Providing on-going staff education (training and printed materials);
- Controlling access to staff by the pharmaceutical industry with its promotional activities;
- Monitoring and taking action to prevent adverse drug reactions and medication errors;
- Providing advice about other drug management issues, such as quality and expenditure.

Governments may encourage hospitals to have DTCs, e.g. by making it an accreditation requirement to various professional societies. DTC members should represent all the major specialities and the administration; they should also be independent and declare any conflict of interest. A senior doctor would usually be the chairperson and the chief pharmacist, the secretary. Factors critical to success include: clear objectives; a firm mandate; support by the senior hospital management; transparency; wide representation; technical competence; a multidisciplinary approach; and sufficient resources to implement the DTC's decisions.

The WHO manual on establishing and running DTCs will be issued in the course on 2003; international two-week training courses are ongoing in Asia and Africa.

WHO database on rational drug use studies

The rational use of medicines was defined by WHO in 1985 as requiring that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time, and at the lowest cost to them and their community. Since that time the International Network for the Rational Use of Drugs (INRUD) has been formed and much has been undertaken by WHO, INRUD and other organizations, to develop and use indicators to monitor drug use and to initiate intervention studies to promote rational use.

However, it is not very well known what the impact of these efforts has been. WHO has recently started the development of a database on rational use of medicines. The objective is to provide a general overview of existing drug use patterns in primary health care settings in developing countries over time, and to study the impact of different types of interventions on improving the use of medicines. Without such information it is difficult to develop a global multifaceted strategy for promotion of rational use of medicines, and to assist regions and countries in prioritizing activities in this area.

Work has started to identifying published and unpublished studies from the INRUD bibliography and WHO reports, and entering the pertinent data concerning prescriber and facility type, disease pattern, methodology and outcome indicators. The data will be analysed by country and region over time (1990-2003) on the impact of different kinds of intervention to promote rational use of medicines. The format of the database is compatible with other WHO databases, to allow for a future analysis of the impact of health systems and policy on the use of medicines. A first analysis of the data will be presented at ICIUM 2004 and is intended as an advocacy tool for promoting rational use of medicines in the developing world.

By March 2002 1160 articles from the INRUD bibliography for 1997-2001 had been screened, and of these, 92 data records had been entered into the database. Future work includes entering the data for the earlier years and a systematic analysis of the data. It is also considered to expand the database in other areas such as hospital-based drug use, self-medication, patients' adherence to treatment and diagnostic accuracy. The database will be made available to interested researchers and policy makers, through the internet.

Summary of recommendations:

The Committee recommended that amodiaquine tablet, 153 mg or 200 mg (base) be added to the core list and its recommended place in curative treatment be further defined by WHO guidelines, that the following note be added: "*amodiaquine should preferably be used as part of combination therapy*" and that the following text be added at the heading of the section: "*Medicines for the treatment of P. falciparum malaria cases should be used in combination.*"

The Committee recommended that azithromycin 250 or 500mg capsule, and suspension 200mg/5ml be added to the core list, for the single dose treatment of genital C.trachomatis infection and of trachoma only; and that the following footnote be added: "*Only listed for single dose treatment of genital C.trachomatis and of trachoma.*"

The Committee recommended that the applications for paediatric ibuprofen, porcine insulin suspension (insulin semilente), miconazole buccal tablets, misoprostol and valaciclovir be rejected.

In considering the use of paracetamol in adults, the Committee recommended that a note be added to the current Model List to state that paracetamol, although listed in section 2.1 (Non-opioid analgesics and antipyretics and nonsteroidal anti-inflammatory drugs) was not recommended for anti-inflammatory use, due to lack of proven benefit to that effect.

The Committee recommended that the 1.5 mg single levonorgestrel be added as a new dosage form of levonorgestrel and that ethinylestradiol + levonorgestrel tablet, 50 micrograms + 250 micrograms (pack of four) be deleted from the list.

The Committee recommended to delete the mention of nonoxinol and spermicides with condoms and diaphragms.

The Committee recommended that the following text be headed at the head of section 6.2.3: *Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour coded blister packs (MDT blister packs) containing standard two medicine (paucibacillary leprosy) or three medicine (multibacillary leprosy) combinations for adult and childhood leprosy should be used. MDT blister packs can be supplied free of charge through WHO.* The committee also

recommended that the same information be included in the WHO Essential Medicines Library and the WHO Model Formulary.

The Committee that the formula of Oral Rehydration Salts be changed to 75 mEq/l sodium (sodium chloride 2.6 g/liter) and 75 mmol/l (13.5 g/liter) glucose and that the following footnote be added: *In cases of cholera a higher concentration of sodium may be required.*

The Committee recommended that the dosage of streptokinase be changed to powder for injection 1.5 million IU in vial.

The Committee recommended that chloral hydrate, dextromethorphan, fludrocortisone, folic acid injection, ipecacuanha syrup and human immunoglobulin be deleted on the basis of the fast-track procedure.

The Committee decided to define the criteria for core and complementary lists, as follows:
*The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost effective medicine for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.*
*The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.*

The Committee recommended that the core and complementary list be combined as one, with medicines on the complementary list printed in italics or otherwise identified.

The Committee recommended that the following medicines be moved from the core list to the complementary list: azathioprine, clomifene, diethylcarbamazine, dopamine, ethosuximide, hydrocortisone rectal preparations, intraperitoneal dialysis solution, methotrexate, penicillamine, pentamidine, pyridostigmine, sulfadiazine and sulfasalazine.

The Committee recommended that the following medicines be moved from the complementary list to the core list: amoxicillin/clavulanic acid, chloramphenicol oily solution, epinephrine (adrenaline) injection, levonorgestrel, mannitol and norethisterone enantate.

The Committee recommended that the following items be deleted from the list: pethidine (due to higher risk of central nervous toxicity when compared with morphine), cyclophosphamide in section 2.4 (due to unfavourable benefit/risk ratio), trimethoprim injection (due to lack of need for this presentation), iron dextran injection (due to unfavourable benefit/risk ratio) and desmopressin (due to rarity of the indication).

The Committee agreed to use the square box symbol on the basis of the following description: *"The square box symbol is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price."*

The Committee recommended that the square box symbol be removed from the following items: amiloride, amoxicillin, amoxicillin/clavulinic acid, antitetanus immunoglobulin, azathioprine, chloramphenicol, chloroquine, ciclosporin, clomifene, charcoal activated, codeine, cycloserine, dexamethasone, diloxanide, DL-methionine, doxorubicin, doxycycline, epinephrine/adrenaline, ethionamide, hydrocortisone, glibenclamide, ibuprofen, mannitol, morphine, neostigmine, promethazine, quinine, sodium nitroprusside, retinol, sulfadiazine, sulfadoxine/pyrimethamine, sulfamethoxazole/trimethoprim and verapamil.

The Committee recommended that the square box symbol be retained but the listed medicine be changed in the following cases: cloxacillin to be replaced by dicloxacillin, captopril to be replaced by enalapril and cimetidine to be replaced by ranitidine.

The Committee recommended that examples of possible alternatives for medicines with a square box symbol should be included in the Essential Medicines Library and the Model Formulary.

The Committee recommended that on the core list, section 3, prednisolone tablets 5mg and 25mg should be the only oral preparation, with a square box and the following footnote: "*There*

is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses". The Committee also recommended that dexamethasone, injection 4mg dexamethasone phosphate (as disodium salt) in 1ml, and hydrocortisone, powder for injection, 100mg (as sodium succinate) in vial both be listed in the same section. On the complementary list, in section 8.3, the same three items should be listed with the same footnote. In section 18.1 all corticosteroids should be deleted, but the section heading should be maintained with the following text added: *Addison's disease is a rare condition; adrenal hormones are already included in section 3.*

The Committee recommended that reserpine, hydralazine and prazosin be deleted from the list, that captopril be replaced by enalapril as the listed example of the therapeutic group, and that a thorough and critical review be carried out of the justification of the use of dihydropyridine calcium channel blockers as first-line treatment for hypertension. The Committee recommended that methyldopa be kept on the core list but that the following note should be added: "*Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.*" The Committee recommended that more research be done on the treatment of hypertension in pregnancy specifically addressing long-term outcomes and child development. In summary, the Committee recommended that boxed atenolol tablet 50mg, 100mg; enalapril tablet 25mg, boxed hydrochlorothiazide scored tablet 25mg, methyldopa tablet 250mg and boxed nifedipine be listed on the core list of section 12.3, and sodium nitroprusside, powder for infusion, 50mg in ampoule on the complementary list.

The Committee recommended that the following items be presented for fast-track deletion at the next Meeting: ether, codeine, colchicine, clonazepam, niclosamide, pyrantel, triclabendazole, oxamniquine, imipenem/cilastatin, nalidixic acid, spectinomycin, levofloxacin, thioacetazone/isoniazid, diethyltoluamide, ergotamine, polygeline, Factors VIII and IX, isoprenaline, procainamide, quinidine, nifedepine, topical sun protection agent, local anaesthetic/astringent ointment, atropine in section 17.4, medroxyprogesterone acetate, silver nitrate eye solution, ergometrine, salbutamol in section 22.2.2, aminophylline, cromoglicic acid, calcium gluconate and sodium fluoride. The Committee recommended that these items be marked in the list with the following footnote: "*The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee*".

Annexes:

Annex 1

Introduction

The concept of essential medicines

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility. Careful selection of a limited range of essential medicines results in a higher quality of care, better management of medicines (including improved quality of prescribed medicines), and more cost-effective use of health resources.

The WHO Model List of Essential Medicines

Most countries require that a pharmaceutical product be approved on the basis of efficacy, safety and quality before it can be prescribed. In addition, the majority of health care and insurance schemes cover only the costs of medicines on a selected list. The medicines on such lists are selected after a study of the medicines used to treat particular conditions, and a comparison of the value they give in relation to their cost. The WHO Model List of Essential Medicines (the "Model List") is an example of such a list. The Model List has been updated every two years since 1977.

The Model List and its procedures are meant as a guide for the development of national and institutional essential medicine lists. It was not designed as a global standard. However, over the past 25 years the Model List has led to a global acceptance of the concept of essential medicines as a powerful means to promote health equity. By the end of 1999, 156 Member States had official essential medicines lists, of which 127 had been updated in the previous five years. Most countries have national lists and some have provincial or state lists as well. National lists of essential medicines usually relate closely to national guidelines for clinical health care practice which are used for the training and supervision of health workers. Lists of essential

medicines also guide the procurement and supply of medicines in the public sector, schemes that reimburse medicine costs, medicine donations, and local medicine production. Many international organizations, including UNICEF and UNHCR, as well as non-governmental organizations and international non-profit supply agencies, have adopted the essential medicines concept and base their medicine supply system mainly on the Model List.

As a model product, the WHO Model List aims to identify cost-effective medicines for priority conditions, together with the reasons for their inclusion, linked to evidence-based clinical guidelines and with special emphasis on public health aspects and considerations of value of money. The information available in the Essential Medicines Library (see below) is specifically aimed to assist national and institutional committees in developing national and institutional lists of essential medicines.

The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost effective medicine for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The **complementary list** presents essential medicines for priority diseases, for which specialised diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The **square box symbol** is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price. Examples of alternatives for the medicines with a square box are not included in the Model List, but additional information is provided in the Essential Medicines Library and the Model Formulary.

The procedures for updating the Model List are in line with the WHO recommended process for developing clinical practice guidelines.[27] Key components are a systematic approach to collecting and reviewing evidence and a transparent development process with several rounds of external review. This process is intended as a model for developing or updating national and institutional clinical guidelines and lists of essential medicines. Detailed information on the process, the information included in the application and the review process are available from the WHO/medicines website (www.who.int/medicines).

Selection criteria

The choice of essential medicines depends on several factors, including the public health relevance and sound and adequate data on the efficacy, safety and comparative cost-effectiveness of available treatments. Stability in various conditions, the need for special diagnostic or treatment facilities and pharmacokinetic properties are also considered if appropriate. When adequate scientific evidence is not available on current treatment of a priority disease, the Expert Committee may either defer the issue until more evidence becomes available, or choose to make recommendations based on expert opinion and experience.

Most essential medicines should be formulated as single compounds. Fixed-ratio combination products are selected only when the *combination* has a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately.

In cost comparisons between medicines, the cost of the total treatment, and not only the unit cost of the medicine, is considered. Cost and cost-effectiveness comparisons may be made among alternative treatments within the same therapeutic group, but will generally not be made across therapeutic categories (for example, between treatment of tuberculosis and treatment of malaria). The absolute cost of the treatment will *not* constitute a reason to exclude a medicine from the Model List that otherwise meets the stated selected criteria. The patent status of a medicine is not considered in selecting medicines for the Model List.

In adapting the WHO Model List to national needs, countries often consider factors such as local demography and pattern of diseases; treatment facilities; training and experience of the available personnel; local availability of individual pharmaceutical products; financial resources; and environmental factors.

[27] Development of WHO Practice Guidelines: Recommended Process. Geneva: WHO, 2001. Document WHO/EIP (October 2001)

The WHO Essential Medicines Library

In addition to the information on whether a medicine is in the Model List or not, it is important for national or institutional selection committees to have access to information that supports the selection of essential medicines, such as summaries of relevant WHO clinical guidelines, the most important systematic reviews, important references and indicative cost information. Other information is also linked to the medicines in the Model List, such as the WHO Model Formulary and information on nomenclature and quality-assurance standards. All this information is presented on the WHO web site as the "WHO Essential Medicines Library" (www.who.int/medicines) intended to facilitate the work of national committees. The library will be further expanded over time.

Quality of products

Priority should be given to ensuring that available medicines have been made according to good manufacturing practices and are of assured quality. Factors that will need to be considered are:

- knowledge of, and confidence in the origin of the product;
- the pharmaceutical stability of the product, particularly in the environment that it will be used;
- where relevant, bioavailability and bioequivalence information

It is recommended that medicines be purchased from known manufacturers, their duly accredited agents, or recognised international agencies known to apply high standards in selecting their suppliers.

Promoting rational use

The selection of essential medicines is only one step to improve the quality of health care. It should be followed by the appropriate use of the selected medicines. Each individual should receive the right medicine, in an adequate dose for an adequate duration, with appropriate information, planning of treatment follow up, and at an affordable cost. In each country and setting, this is influenced by a number of factors, such as regulatory decisions, procurement, information, training, and the context where medicines are prescribed or recommended.

Training, education and the provision of medicines information

For the safe, effective and prudent use of essential medicines, relevant, reliable and independent medicines information should be available. Health care professionals should receive education about the use of medicines not only during their training but also throughout their careers. More highly trained individuals should be encouraged to assume a responsibility to educate those with less training. Health care providers and responsible for dispensing medicines should take 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 medicines information issues. Problem-based pharmacotherapy teaching[28] has been shown to be an effective strategy in this area.

Appropriate medicines information that is well presented ensures that medicines are used properly and decreases inappropriate medicine use. Ministries of Health must take the responsibility for arranging for the provision of such information. Independent medicine information activities should be properly funded and if necessary financed through health care budgets. Electronic, readily accessible sources of medicines information are becoming available in many settings and can be the basis of reliable medicines information systems.

Standard clinical guidelines

Standard clinical guidelines are an effective tool for assisting health professionals to choose the most appropriate medicine for a given patient with a given condition. STGs should be developed at national and local level and updated on a regular basis. It is not sufficient to develop standard clinical guidelines without an education and training program to encourage their use.

Drugs and Therapeutic Committees

Drugs and Therapeutic Committees should play an important role in helping to develop and implement an effective essential medicines program. These committees should be encouraged to select products for local use from a national essential medicines list, to measure and monitor the

use of medicines in their own environments and undertake interventions to improve medicines use. There is good evidence that involving Drugs and Therapeutic Committees and prescribers in guideline development can contribute to improving prescribing behaviour.

Measuring and monitoring use

Drug utilisation studies are those dealing with the development, regulation, marketing, distribution, prescription, dispensing, and use of medicines in a society, with special emphasis on the resulting medical, social and economic consequences. These studies can examine any level of the therapeutic chain, from medicines development to their actual use by people. They can provide consumption indicators in a given country, area or institution. Consumption can be quantified as economic expenditure (either in absolute terms or as percentage of total health budget), as number of units, or as defined daily doses[29] (old reference 31). They can aim at describing the consumption of all medicines, or of particular groups of medicines or therapeutic areas. The Anatomical Therapeutic Chemical (ATC) classification is a useful tool for international comparisons on the use of medicines. Drug utilisation studies can be medicine-oriented (on the use of a particular medicine or group of medicines), or problem-oriented (on the treatment of a particular condition or disease).

The *efficacy* of a medicine is most reliably defined on the basis of randomised clinical trials, which, if well conducted, provide the most reliable estimates of the treatment effect of a new medicine. Clinical trials cannot be conducted in all possible populations or settings and their results should therefore be carefully translated into routine clinical practice. Drug utilisation studies aim at providing evidence on the use and the effects of medicines in routine conditions, and they thus can provide additional evidence for the evaluation of *effectiveness*.

Such studies are important tools for identifying those factors or elements of the therapeutic chain in need of improvement or change. The results should be taken into consideration when taking regulatory action, selecting medicines, information, training, and teaching. Institutional and local drug and therapeutic committees should set up drug utilisation studies and other methods for the surveillance of the use of medicines and of its effects.

Monitoring of drug safety and pharmacovigilance

[28] *Guide to Good Prescribing*. Geneva: World Health Organization, 1994. Document WHO/DAP/94.11

[29] Guidelines for ATC classification and DDD assignment, 5th ed. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2001

The surveillance of the safety of medicines is part of the general surveillance of their use. The aims of the various forms of pharmacovigilance are to identify new, previously unrecognised adverse effects of medicines, to quantify their risks, and to communicate with drug regulatory authorities, health professionals, and, when relevant, with the public. Voluntary reporting of adverse effects of medicines, on which the International WHO Programme for Drug Monitoring is based, has been effective in identifying a number of previously undiscribed effects. Voluntary reporting schemes and other methods for assembling case series can identify certain local safety problems, and may be the basis for specific regulatory or educational interventions. The magnitude of the risk of adverse effects is generally evaluated with observational epidemiological methods, such as case-control, cohort, and case-population studies. Each country and institution should set up simple schemes aimed at identifying problems related with the safety of medicines.

13th Model List of Essential Medicines

(one list, with complementary medicines in italics)

proffered

Summary of recommendations:

The Committee recommended that amodiaquine tablet, 153 mg or 200 mg (base) be added to the core list and its recommended place in curative treatment be further defined by WHO guidelines, that the following note be added: "*amodiaquine should preferably be used as part of combination therapy*" and that the following text be added at the heading of the section: "*Medicines for the treatment of P. falciparum malaria cases should be used in combination.*"

The Committee recommended that azithromycin 250 or 500mg capsule, and suspension 200mg/5ml be added to the core list, for the single dose treatment of genital C.trachomatis infection and of trachoma only; and that the following footnote be added: "*Only listed for single dose treatment of genital C.trachomatis and of trachoma.*"

The Committee recommended that the applications for paediatric ibuprofen, porcine insulin suspension (insulin semilente), miconazole buccal tablets, misoprostol and valaciclovir be rejected.

In considering the use of paracetamol in adults, the Committee recommended that a note be added to the current Model List to state that paracetamol, although listed in section 2.1 (Non-opioid analgesics and antipyretics and nonsteroidal anti-inflammatory drugs) was not recommended for anti-inflammatory use, due to lack of proven benefit to that effect.

The Committee recommended that the 1.5 mg single levonorgestrel be added as a new dosage form of levonorgestrel and that ethinylestradiol + levonorgestrel tablet, 50 micrograms + 250 micrograms (pack of four) be deleted from the list.

The Committee recommended to delete the mention of nonoxinol and spermicides with condoms and diaphragms.

The Committee recommended that the following text be headed at the head of section 6.2.3: *Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance. Colour coded blister packs (MDT blister packs) containing standard two medicine (paucibacillary leprosy) or three medicine (multibacillary leprosy) combinations for adult and childhood leprosy*

should be used. MDT blister packs can be supplied free of charge through WHO. The committee also recommended that the same information be included in the WHO Essential Medicines Library and the WHO Model Formulary.

The Committee that the formula of Oral Rehydration Salts be changed to 75 mEq/l sodium (sodium chloride 2.6 g/liter) and 75 mmol/l (13.5 g/liter) glucose and that the following footnote be added: *In cases of cholera a higher concentration of sodium may be required.*

The Committee recommended that the dosage of streptokinase be changed to powder for injection 1.5 million IU in vial.

The Committee recommended that chloral hydrate, dextromethorphan, fludrocortisone, folic acid injection, ipecacuanha syrup and human immunoglobulin be deleted on the basis of the fast-track procedure.

The Committee decided to define the criteria for core and complementary lists, as follows:
*The **core list** presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost effective medicine for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.*
*The **complementary list** presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.*

The Committee recommended that the core and complementary list be combined as one, with medicines on the complementary list printed in italics or otherwise identified.

The Committee recommended that the following medicines be moved from the core list to the complementary list: azathioprine, clomifene, diethylcarbamazine, dopamine, ethosuximide, hydrocortisone rectal preparations, intraperitoneal dialysis solution, methotrexate, penicillamine, pentamidine, pyridostigmine, sulfadiazine and sulfasalazine.

The Committee recommended that the following medicines be moved from the complementary list to the core list: amoxicillin/clavulanic acid, chloramphenicol oily

solution, epinephrine (adrenaline) injection, levonorgestrel, mannitol and norethisterone enantate.

The Committee recommended that the following items be deleted from the list: pethidine (due to higher risk of central nervous toxicity when compared with morphine), cyclophosphamide in section 2.4 (due to unfavourable benefit/risk ratio), trimethoprim injection (due to lack of need for this presentation), iron dextran injection (due to unfavourable benefit/risk ratio) and desmopressin (due to rarity of the indication).

The Committee agreed to use the square box symbol on the basis of the following description: *"The square box symbol is primarily intended to indicate similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price."*

The Committee recommended that the square box symbol be removed from the following items: amiloride, amoxicillin, amoxicillin/clavulinic acid, antitetanus immunoglobulin, azathioprine, chloramphenicol, chloroquine, ciclosporin, clomifene, charcoal activated, codeine, cycloserine, dexamethasone, diloxanide, DL-methionine, doxorubicin, doxycycline, epinephrine/adrenaline, ethionamide, hydrocortisone, glibenclamide, ibuprofen, mannitol, morphine, neostigmine, promethazine, quinine, sodium nitroprusside, retinol, sulfadiazine, sulfadoxine/pyrimethamine, sulfamethoxazole/trimethoprim and verapamil.

The Committee recommended that the square box symbol be retained but the listed medicine be changed in the following cases: cloxacillin to be replaced by dicloxacillin, captopril to be replaced by enalapril and cimetidine to be replaced by ranitidine.

The Committee recommended that examples of possible alternatives for medicines with a square box symbol should be included in the Essential Medicines Library and the Model Formulary.

The Committee recommended that on the core list, section 3, prednisolone tablets 5mg and 25mg should be the only oral preparation, with a square box and the following footnote: "*There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses*". The Committee also recommended that dexamethasone, injection 4mg dexamethasone phosphate (as disodium salt) in 1ml, and hydrocortisone, powder for injection, 100mg (as sodium succinate) in vial both be listed in the same section. On the complementary list, in section 8.3, the same three items should be listed with the same footnote. In section 18.1 all corticosteroids should be deleted, but the section heading should be maintained with the following text added: *Addison's disease is a rare condition; adrenal hormones are already included in section 3.*

The Committee recommended that reserpine, hydralazine and prazosin be deleted from the list, that captopril be replaced by enalapril as the listed example of the therapeutic group, and that a thorough and critical review be carried out of the justification of the use of dihydropyridine calcium channel blockers as first-line treatment for hypertension. The Committee recommended that methyldopa be kept on the core list but that the following note should be added: "*Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines.*" The Committee recommended that more research be done on the treatment of hypertension in pregnancy specifically addressing long-term outcomes and child development. In summary, the Committee recommended that boxed atenolol tablet 50mg, 100mg; enalapril tablet 25mg, boxed hydrochlorothiazide scored tablet 25mg, methyldopa tablet 250mg and boxed nifedipine be listed on the core list of section 12.3, and sodium nitroprusside, powder for infusion, 50mg in ampoule on the complementary list.

The Committee recommended that the following items be presented for fast-track deletion at the next Meeting: ether, codeine, colchicine, clonazepam, niclosamide, pyrantel, triclabendazole, oxamniquine, imipenem/cilastatin, nalidixic acid, spectinomycin, levofloxacin, thioacetazone/isoniazid, diethyltoluamide, ergotamine, polygeline, Factors VIII and IX, isoprenaline, procainamide, quinidine, nifedepine, topical sun protection agent, local anaesthetic/astringent ointment, atropine in section 17.4, medroxyprogesterone acetate, silver

nitrate eye solution, ergometrine, salbutamol in section 22.2.2, aminophylline, cromoglicic acid, calcium gluconate and sodium fluoride. The Committee recommended that these items be marked in the list with the following footnote: "*The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee*".

Go back to previous page

WHO Model List of Essential Medicines in alphabetical order

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

A

abacavir
acetazolamide
acetylcysteine
acetylsalicylic acid
aciclovir
albendazole
alcuronium
allopurinol
aluminium diacetate
aluminium hydroxide
amidotrizoate
amikacin
amiloride
aminophylline
aminosalicylic acid (p-aminosalicylic acid)
amitriptyline
amodiaquine
amoxicillin
amoxicillin + clavulanic acid
amphotericin B
ampicillin
anti-D immunoglobulin (human)
antihaemorrhoidal medicine - local anaesthetic, astringent and anti-inflammatory medicine
antitetanus immunoglobulin (human)
antivenom serum
artemether
artemether + lumefantrine
artesunate
ascorbic acid
asparaginase
atenolol
atropine
azathioprine
azithromycin

B

barium sulfate
BCG vaccine
beclometasone
benzathine benzylpenicillin
benznidazole
benzoic acid + salicylic acid
benzoyl peroxide
benzyl benzoate
benzylpenicillin
betamethasone
biperiden
bleomycin
bupivacaine

C

calamine lotion
calcium folinate
calcium gluconate
cancer - drugs for pain relief
capreomycin
captopril
carbamazepine
ceftazidime
ceftriaxone
charcoal, activated
chloral hydrate
chlorambucil
chloramphenicol
chlorhexidine
chlorine base compound
chlormethine
chloroquine
chloroxylenol
chlorphenamine
chlorpromazine
ciclosporin
cimetidine
ciprofloxacin
cisplatin
clindamycin
clofazimine
clomifene
clomipramine
clonazepam

cloxacillin
coal tar
codeine
colchicine
condoms
copper-containing intrauterine device
cromoglicic acid
cyclophosphamide
cycloserine
cytarabine

D
dacarbazine
dactinomycin
dapsone
daunorubicin
deferoxamine
desmopressin
dexamethasone
dextran 70
dextromethorphan
diaphragms
diazepam
didanosine (ddI)
diethylcarbamazine
diethyltoluamide
digoxin
diloxanide
dimercaprol
diphtheria antitoxin
diphtheria vaccine
dithranol
dopamine
doxorubicin
doxycycline

E
efavirenz (EFV or EFZ)
eflornithine
ephedrine
epinephrine (adrenaline)
ergocalciferol
ergometrine
ergotamine

erythromycin
ethambutol
ethanol
ether, anaesthetic
ethinylestradiol
ethinylestradiol + levonorgestrel
ethinylestradiol + norethisterone
ethionamide
ethosuximide
etoposide

F

factor IX complex concentrate (coagulation factors, II, VII, IX, X)*
factor VIII concentrate
ferrous salt
ferrous salt + folic acid
fluconazole
flucytosine
fludrocortisone
fluorescein
fluorouracil
fluphenazine
folic acid
furosemide

G

gentamicin
glibenclamide
glucose
glucose with sodium chloride
glutaral
glyceryl trinitrate
griseofulvin

H

haloperidol
halothane
heparin sodium
hepatitis B vaccine
hydralazine
hydrochlorothiazide
hydrocortisone
hydroxocobalamin

I

ibuprofen
idoxuridine
imipenem + cilastatin
immunoglobulin, human normal
indinavir (IDV)
influenza vaccine
insulin (intermediate-acting)
insulin (soluble)
intraperitoneal dialysis solution (of appropriate composition)
iodine
iohexol
iopanoic acid
ipecacuanha
ipratropium bromide
iron dextran
isoniazid
isoniazid + ethambutol
isoprenaline
isosorbide dinitrate
ivermectin

K

kanamycin
ketamine

L

lamivudine (3TC)
levamisole
levodopa + carbidopa
levofloxacin
levonorgestrel
levothyroxine
lidocaine
lidocaine + epinephrine (adrenaline)
lipid-lowering agents
lithium carbonate
lopinavir + ritonavir (LPV/r)

M

magnesium hydroxide
magnesium sulfate
mannitol

P

paracetamol
penicillamine
pentamidine
permethrin
pertussis vaccine
pethidine
phenobarbital
phenoxymethylpenicillin
phenytoin
phytomenadione
pilocarpine
plasma fractions
podophyllum resin
poliomyelitis vaccine
polygeline
polyvidone iodine
potassium chloride
potassium ferric hexacyanoferrate (II)2H20 (Prussian blue)
potassium iodide
potassium permanganate
praziquantel
prazosin
prednisolone
primaquine
procainamide
procaine benzylpenicillin
procarbazine
proguanil
promethazine
propranolol
propyliodone
propylthiouracil
protamine sulfate
pyrantel
pyrazinamide
pyridostigmine
pyridoxine
pyrimethamine

Q

quinidine
quinine

measles vaccine
mebendazole
medroxyprogesterone acetate
mefloquine
meglumine antimoniate
meglumine iotroxate
melarsoprol
meningococcal meningitis vaccine
mercaptopurine
metformin
methionine (DL-methionine)
methotrexate
methyldopa
methylrosanilinium chloride (gentian violet)
methylthioninium chloride (methylene blue)
metoclopramide
metronidazole
miconazole
morphine
mumps vaccine

N

nalidixic acid
naloxone
nelfinavir (NFV)
neomycin + bacitracin
neostigmine
nevirapine (NVP)
niclosamide
nicotinamide
nifedipine
nifurtimox
nitrofurantoin
nitrous oxide
norethisterone
norethisterone enantate
nystatin

O

ofloxacin
oral rehydration salts (for glucose-electrolyte solution)
oxamniquine
oxygen
oxytocin

R

rabies immunoglobulin
rabies vaccine (inactivated: prepared in cell culture)
reserpine
retinol
riboflavin
rifampicin
rifampicin + isoniazid
rifampicin + isoniazid + pyrazinamide
rifampicin + isoniazid + pyrazinamide + ethambutol
ritonavir (r)
rubella vaccine

S

salbutamol
salicylic acid
saquinavir (SQV)
selenium sulfide
senna
silver nitrate
silver sulfadiazine
sodium calcium edetate
sodium chloride
sodium fluoride
sodium hydrogen carbonate
sodium lactate (compound solution)
sodium nitrite
sodium nitroprusside
sodium thiosulfate
spectinomycin
spironolactone
stavudine (d4T)
streptokinase
streptomycin
sulfadiazine
sulfadoxine + pyrimethamine
sulfamethoxazole with trimethoprim
sulfasalazine
suramin sodium
suxamethonium

T
tamoxifen
testosterone
tetanus vaccine
tetracaine
tetracycline
theophylline
thiamine
thioacetazone + isoniazid
thiopental
timolol
triclabendazole
trimethoprim
tropicamide
tuberculin, purified protein derivative (PPD)
typhoid vaccine

U
ultraviolet-blocking agent - topical sun protection agent with activity against ultraviolet A and ultraviolet B
urea

V
valproic acid
vancomycin
vecuronium
verapamil
vinblastine
vincristine

W
warfarin
water for injection

Y
yellow fever vaccine

Z
zidovudine (ZDV or AZT)
ZZZ