

THE SELECTION AND USE OF ESSENTIAL MEDICINES

Report of the WHO Expert Committee, 2007
(including the 15th Model List of Essential Medicines)



**World Health
Organization**

The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications. The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences. To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective — the attainment by all people of the highest possible level of health.

The WHO Technical Report Series makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO. An annual subscription to this series, comprising about six such reports, costs CHF 168.00/US\$ 151.00 (CHF 128.40/US\$ 115.00 in developing countries). For further information, please contact: WHO Press, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland (tel. +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int; order on line: <http://www.who.int/bookorders>).

This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

WHO Technical Report Series

946

THE SELECTION AND USE OF ESSENTIAL MEDICINES

Report of the WHO Expert Committee, 2007
(including the 15th Model List of Essential Medicines)



**World Health
Organization**

WHO Library Cataloguing-in-Publication Data

WHO Expert Committee on the Selection and Use of Essential Medicines
(15th: 2007: Geneva, Switzerland)

The selection and use of essential medicines: report of the WHO Expert Committee, 2007:
(including the 15th model list of essential medicines).

(WHO technical report series; no. 946)

1. Essential drugs - standards. 2. Formularies - standards. 3. Drug information services
- organization and administration. 4. Drug utilization. 5. Pharmaceutical preparations
- classification. 6. Guidelines. I. Title. II. Title: 15th model list of essential medicines.
III. Series.

ISBN 978 92 4 120946 5
ISSN 0512-3054

(LC/NLM classification: QV 55)

© **World Health Organization 2007**

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications — whether for sale or for noncommercial distribution — should be addressed to WHO Press, at the above address (fax: +41 22 791 4806; e-mail: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

**Typeset in Switzerland
Printed in Switzerland**

Contents

1. Introduction	1
2. Open session	2
3. Update on current activities	4
3.1 Procedure to update and disseminate the Model List	4
3.2 Proposal for subcommittee on essential medicines for children	6
3.3 Proposal on listing fixed-dose combination products for infectious diseases	8
3.4 Report from the Advisory Committee on Safety of Medicinal Products	10
3.5 Update of dosage forms and strengths for products on the Model List	10
3.6 Rare diseases proposal	12
3.7 Procedure for updating the content of the Interagency Emergency Health Kit	13
3.8 Late agenda item on medicines for acute care	14
3.9 Report on WHO Model Formulary	14
3.10 Report on Drug Bulletin manual	15
3.11 Review of proposal regarding critically important antibiotics	15
3.12 Advice on draft resolution on rational use of medicines	16
4. Changes made in revising the Model List by section: medicines for all populations	18
4.1 Section 2: addition of prolonged-release morphine	18
4.2 Section 6.1: deletion of levamisole as anthelmintic	19
4.3 Section 6.2.1: Beta lactam: addition of cefazolin/cefalexin	20
4.4 Section 6.2.4: Antituberculosis medicines	22
4.5 Section 6.4.2: Antiretrovirals	24
4.6 New section under 6.4.3: Addition of new section and medicine ribavirin	35
4.7 Late item: antiviral medicines for pandemic influenza	35
4.8 Section 6.5.2: Antileishmaniasis: addition of paromomycin	36
4.9 Section 6.5.3: Antimalarial medicines	37
4.10 Review of Section 6.5.5: Antitrypanosomal medicines	40
4.11 Section 7: Antimigraine medicines	42
4.12 Section 8.2: Cytotoxic drugs	44
4.13 Review of section 8.4: Medicines used in palliative care	45
4.14 Section 12.6: Lipid-lowering drugs: addition of simvastatin	46
4.15 Section 18.3: Contraceptives	48
4.16 Section 19.2: Sera and immunoglobulins	52
4.17 Review of section 19.3: Vaccines	54
4.18 Section 21.1: Ophthalmological preparations – Anti-infective agents	56
4.19 Section 24: Psychotherapeutic medicines – 24.2.1: Medicines used in depressive disorders	58

5.	Paediatric medicines	59
5.1	Section 5: Anticonvulsants/antiepileptics	59
5.2	Section 6.2.4: Antituberculosis medicines	62
5.3	Section 6.5.3: Antimalarial medicines	63
5.5	Section 25: Medicines acting on the respiratory tract	64
5.6	Section 27: Vitamins and minerals	65
6.	Summary of recommendations – additions, changes and deletions to the Model List	66
	References	70
	Annex 1	
	Declaration of interests of Committee Members	79
	Annex 2	
	The 15th WHO Model List of Essential Medicines	81
	Annex 3	
	The Anatomical Therapeutic Chemical (ATC) classification system	117
	Annex 4	
	Alphabetical list of essential medicines (with ATC classification code numbers)	138
	Annex 5	
	Proposed procedure to update and disseminate the WHO Model List of Essential Medicines	146
	Annex 6	
	Revised procedure for updating the content of the Interagency Emergency Health Kit	152

WHO Expert Committee on the Selection and Use of Essential Medicines

Geneva, 19–23 March 2007

Members

- Dr Lisa Bero, (Rapporteur), University of California, San Francisco, CA, USA
- Dr Noël Cranswick, Director, Clinical Pharmacology, Royal Children's Hospital, Parkville, Victoria, Australia
- Dr Rohini Fernandopulle, Senior Lecturer, Department of Pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka
- Dr Anwar-ul Hassan Gilani, National Professor of Pharmacology, Department of Biological and Biomedical Sciences, Faculty of Health Sciences, The Aga Khan University, Karachi, Pakistan
- Dr Usha Gupta, Delhi Society for Promotion of Rational Use of Drugs, Delhi Government Dispensary, New Delhi, India
- Dr Abdelkader Helali, Director, Centre National de Pharmacovigilance et Matériovigilance, Ministère de la Santé et de la Population, Alger, Algeria
- Dr Alar Irs, Deputy Director-General, State Agency of Medicines, University of Tartu, Tartu, Estonia
- Dr Youping Li, Chinese Cochrane Centre, West China Hospital, Sichuan University, Chengdu, People's Republic of China
- Dr Liliana de Lima, Executive Director, International Association for Hospice and Palliative Care, Houston, TX, USA
- Mr Dinesh Mehta, Executive Editor, British National Formulary, Royal Pharmaceutical Society of Great Britain, London, England
- Dr Marcus M. Reidenberg, (Chair), Chief, Division of Clinical Pharmacology, Weill Medical College of Cornell University, New York, NY, USA
- Dr Sri Suryawati, Director, Centre for Clinical Pharmacology and Medicine Policy Studies, Gadjah Mada University, Yogyakarta, Indonesia
- Dr Susan Walters, Lyons, ACT, Australia
- Dr Lenita Wannmacher, Department of Clinical Pharmacology, School of Medicine, University of Passo Fundo, Rio Grande do Sul, Brazil

Temporary advisers

- Professor Hany Abdel-Aleem, Department of Obstetrics and Gynecology, Assiut University Hospital, Assiut, Egypt
- Dr Albert Figueras, Fundació Institut Català de Farmacologia, Servei de Farmacologia Clínica, Hospital Vall d'Hebron, Barcelona, Spain
- Mr Andy Gray, Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa

Dr Estrella Paje-Villar, Professor of Paediatrics and Pharmacology, Faculty of Medicine, University of Sto. Tomas, Sampaloc, Manila, Philippines

Dr Thamizhanban Pillay, Pharmaceutical Economic Evaluation, National Department of Health, Pretoria, South Africa

Representatives of other organizations

United Nations Children's Fund (UNICEF)

Dr Hanne Bak Pedersen, UNICEF Supply Division, Copenhagen, Denmark

United Nations Population Fund (UNFPA)

Dr Lindsay Edouard, Senior Adviser, Reproductive Health Branch, United Nations Population Fund, New York, USA

Secretariat

Dr Suzanne Hill, Scientist, Policy, Access and Rational Use (PAR)/Medicines Policy and Standards (PSM) and Secretary of the WHO Expert Committee on the Selection and Use of Essential Medicines, WHO, Geneva, Switzerland

Dr Hans V. Hogerzeil, Director, Medicines Policy and Standards (PSM), WHO, Geneva, Switzerland

Dr Clive Ondari, Coordinator, Policy, Access and Rational Use (PAR)/Medicines Policy and Standards (PSM), WHO, Geneva, Switzerland

Dr Jane Roberston, Policy, Access and Rational Use (PAR)/Medicines Policy and Standards (PSM), WHO, Geneva, Switzerland

Dr Budiono Santoso, Health Technology and Pharmaceuticals, Health Sector Development, DHS/PHA, WHO Regional Office for the Western Pacific (WPRO), Manila, Philippines

Dr Lilia Ziganshina, Policy, Access and Rational Use (PAR)/Medicines Policy and Standards (PSM), WHO, Geneva, Switzerland

Dr Howard Zucker, Assistant Director-General, Health Technology and Pharmaceuticals (HTP Cluster), WHO, Geneva, Switzerland

1. Introduction

The WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 19 to 23 March 2007. The meeting was opened on behalf of the Director-General by Dr Howard Zucker, Assistant Director-General for Health Technology and Pharmaceuticals. He stated that WHO's medicines programme is very important to Member States and that the recommendations made by its Expert Committees were critical. He briefly explained some aspects of the Committee procedures. He stated that the Committee is not a representative one, that all members participated in their personal capacity and are not allowed to take instructions from any government or any other authority. (See Annex 1 for Committee members' declarations of interest.)

Prior to the open session, Dr Hans V. Hogerzeil, Director of the Department of Medicines Policy and Standards, addressed the Committee. He noted that this would be the fourth meeting of the Expert Committee operating under the new procedures approved in 2002 and that the early posting of most documents on the web site, together with the rounds of review and comments prior to the meeting ensured the transparency of the process. Dr Hogerzeil also noted that this year is the 30th anniversary of the Essential Medicines List, and that it was timely to examine the future role of the list particularly in the context of supporting primary health care, identified by the Director-General as a priority for WHO.

The WHO Secretariat requested and received agreement from the Committee to hold an open session as part of its meeting (see section 2). The purpose of the open session was to allow all stakeholders to participate in the discussions and to comment on issues relating to the WHO Model List of Essential Medicines. Furthermore, for members of the Expert Committee it provides an opportunity to receive, at first-hand, additional information and opinion on matters under consideration. Discussions and opinions put forward during the open session are reflected in the report of the meeting.

The Committee decided to maintain the reporting format adopted at previous meetings. A summary of the Committee's deliberations on each of the items under discussion is presented in the main body of the report. The updated version of the Model List (the 15th Model List), including a general introduction and explanatory notes, is presented in Annex 2. This Annex is also posted on the WHO web site and available in printed form in all six official languages of the Organization. A list of items on the Model List ordered by their corresponding Anatomical Therapeutic Chemical (ATC) classification code number(s) is attached as Annex 3.

The full texts of the applications for changes, additions or deletions with all the evidence and references, as well as the external reviews and comments

received, are not included in this report but remain available on the WHO web site, and are accessible through the Essential Medicines Library (<http://mednet3.who.int/EMLib/>). Information on medicines deleted from the Model List in the past is retained in a separate section of the library.

2. **Open session**

The open session of the meeting was opened by Dr Howard Zucker, on behalf of the Director-General. He stated that all information submitted to the Committee in support of the evidence-based decisions would be placed in the public domain through the WHO web site. He reminded participants that all comments made during the open session would be noted and taken into consideration by the Committee when formulating final recommendations in subsequent private sessions.

Dr Zucker noted that 2007 was the 30th year of the Essential Medicines List. It was appropriate that in the 30th year, the 120th session of the WHO Executive Board had adopted two important draft resolutions in relation to medicines that would be discussed by the Committee. One resolution recommended an approach to rational use of medicines and the second recommended a programme of activities to improve medicines for children. Dr Zucker requested the Committee to give careful consideration to the proposal for a formal subcommittee to establish a list of essential medicines for children.

As part of the open session, participants were briefed about various activities relating to the Model List (see Section 3).

A number of issues were raised and debated during the open session.

HIV

The participants were informed about the current public health approach being used by the WHO HIV/AIDS Department. Professor Gilks described this as “managed public sector care”, with the aim of scaling up the programme on the basis of the principles of universal access and limited choices rather than based on the needs of individual patients. He outlined guidelines developed by the Department in 2006, the strategic and programmatic importance of fixed-dose combinations to increase adherence to medication regimens, to decrease pill burden and, over time, to contribute to reduced drug resistance. The methods being used by the HIV/AIDS Department to identify the preferred treatment options were outlined.

Safety

A representative from the Quality Assurance and Safety: Medicines (QSM) team presented a summary of the fourth meeting of the WHO Advisory

Committee on the Safety of Medicinal Products (ACSoMP) held in February 2007. Key discussion points for the meeting were a strategy document for safety of medicines, a document on promoting the safety of medicines used to treat children and preparation of an advocacy document for pharmacovigilance. The QSM team had prepared documents addressing safety issues relevant to a number of applications under consideration by the Expert Committee.

International Union of Basic and Clinical Pharmacology

A presentation was made to the Committee on behalf of the Paediatric Subcommittee of the Clinical Pharmacology Division of the International Union of Basic and Clinical Pharmacology (IUPHAR), describing children as a neglected population. Children are “neglected” in the sense that they do not have access to treatment with medicinal products that meet the same standards of quality, safety and efficacy as the treatments available to adults, although international agreements on human rights give children the right to the same level of health and health care enjoyed by others. The presentation highlighted the challenges of developing medicines for children, and the need to recognize five phases of development, each of which differed with regard to metabolism and drug handling. Progress had been made within the regulatory authorities in the USA and the European Union (EU), reflecting a commitment to the development of medicines for children. IUPHAR has formed a number of Paediatric Expert Groups at the European Agency for the Evaluation of Medical Products (EMA) in the last three years to assess the needs of children in major clinical areas.

Médecins Sans Frontières

The Committee was informed about the Médecins Sans Frontières Campaign for Access to Essential Medicines. Médecins Sans Frontières supported the initiative to create an Essential Medicines List for children, encouraged WHO to accelerate the publication of this list, and urged WHO to ensure that the research and development of products for children takes place. Médecins Sans Frontières acknowledged the importance of fixed-dose combinations in the treatment of AIDS and commented on specific applications to be considered by the Expert Committee (fixed-dose combinations for HIV/AIDS and antitrypanosomal medicines). Médecins Sans Frontières recognized the role of listing medicines on the Model List in creating an incentive for producers and providers to improve the quality of a product. Médecins Sans Frontières urged the Committee not to consider the cost of a product in its deliberations.

International Society of Paediatric Oncology

A written statement was provided to the Committee by the President of the International Society of Paediatric Oncology (SIOP). The President

expressed the Society's commitment to an Essential Medicines List for Children and requested that the Society be able to participate in the deliberations with WHO. The Society recognized that about 80% of children worldwide who develop cancer currently do not receive optimal care and often do not even receive any supportive or palliative care. The Society has identified a number of important steps required to make progress in the area of improved oncology and palliative care medicines for children. It wishes to encourage countries to adopt the principle of dedicated specialist units to concentrate expertise, reduce wastage and improve survival and quality of life of children with life-threatening conditions.

Polyvalent human immunoglobulins

Representatives from Chandigarh Hospital, India, and the Primary Immunodeficiency Association, England, addressed the Committee on the application for the reinstatement of polyvalent human immunoglobulins (IGs). They outlined the role of IGs as replacement therapy for primary immunodeficiency disorders, a number of which occurred in children, and as immunomodulatory agents. The representative from Chandigarh Hospital addressed what he described as misunderstandings about the treatment of these diseases, pointing out that without IGs morbidity and mortality from these conditions were substantial. The representative of the Primary Immunodeficiency Association spoke as a patient and reiterated the statements of his co-speaker and suggested that his own experience illustrated the efficacy and safety of IGs and the value of treatment with them.

Additional comments

Discussion was invited on the matters raised in the open session. The IUPHAR representative provided further comments on paediatric medicines. Comments on the application for immunoglobulins were made on behalf of the International Patient Organisation for Primary Immunodeficiencies (IPOPI). A representative of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) stressed the importance of the Committee considering the availability of quality products in its deliberations. Support from Health Action International (HAI) for the establishment of a steering group to engage stakeholders as part of the Rational Use of Medicines proposal was expressed.

3. Update on current activities

3.1 Procedure to update and disseminate the Model List

The current "Procedure to update and disseminate the WHO Model List of Essential Medicines" was approved by the Executive Board in 2001 and

has been used by the Expert Committee on Selection and Use of Essential Medicines since that time. The Committee has now had considerable experience in the use of these procedures, and some changes have been made as experience in evidence-based selection of medicines has developed. The Secretariat therefore proposed an update to the “Procedure” to reflect that experience. The amendments are generally minor and reflect the methods of reviewing applications and seeking public comment through the web site, as well as the need to ensure that adequate information is provided about each medicine in an application.

The Committee supported the proposed updates and recommended that the Secretariat take appropriate steps to finalize them.

3.1.2 **Procedure for between-meeting decisions**

The WHO Expert Committee on Selection and Use of Essential Medicines has met nearly every two years since it was first established in 1977. In accordance with the WHO Regulations for Expert Advisory Panels and Expert Committees, the report of each committee has been finalized at the end of its meeting. No between-meeting decisions have been taken so far, although occasionally changes have been made to the report of the meeting and its recommendations after the conclusion of the meeting, based on written approval by all Expert Committee members.

A number of other WHO programmes are reliant to a greater or lesser extent on the Model List of Essential Medicines. In particular, the programmes on HIV/AIDS, malaria and tuberculosis (TB) link their procured medicines closely to those included on the Model List, and the Prequalification Programme also considers whether a medicine is on the Model List when specifying the “Expressions of Interest” for its programme. In these areas, and in the area of emerging diseases, there is an increasing need to update the Model List more often than every two years.

The Regulations do not specify the methods for making decisions between formal meetings of the Committee. To accommodate the possibility of between-meeting decisions being required, it is therefore proposed to have the Committee adjourn at the end of its formal meeting and formally remain in existence until the next Committee is appointed.

The Committee supported the need for making decisions about amending the Model List more often than every two years. The “between meetings” proposal of the Secretariat was one option but the Committee recommended that other options, such as more frequent meetings or virtual meetings, should also be considered.

The Committee discussed whether regulatory approval of a medicine would be a prerequisite for its inclusion in the Model List. Although the decision

to include a medicine in the Model List is generally post-regulatory, this may not always be possible.

3.2 **Proposal for subcommittee on essential medicines for children**

In August 2006, a joint WHO–UNICEF expert consultation on essential medicines for children was held to review some of the problems associated with access to essential medicines for children. The report of the meeting is available at: <http://www.who.int/medicines/publications/UNICEFconsultation.pdf>

The meeting produced a list of recommended actions to be undertaken by WHO and UNICEF to improve access to essential medicines for children. One of the key recommendations was to update the WHO Model List of Essential Medicines to include essential medicines for children, based on their clinical needs and the burden of disease.

In January 2007, the 120th Session of the Executive Board of the World Health Assembly (WHA) adopted a draft resolution (EB120.13) requesting the Director-General and Member States to take action to make available better medicines for children. This resolution outlines a comprehensive programme for the work needed.

The WHO Secretariat has commissioned a number of preliminary papers as part of the evidence needed to support the recommendation for updating the Model List to meet the needs of children. In so doing, it has become clear that developing an up-to-date list of essential medicines for children is likely to require additional meetings of appropriate experts, as there is more work than can be completed as part of the usual agenda of the regular meetings of the Expert Committee. There are several reasons for this. The technical scope of the work needed requires additional consultation and time, for example, for developing the criteria for defining essential medicines for children, including defining age groups within “childhood”, as different age groups have different patterns of disease and different needs. A position statement on the types of dosage form to be defined as “essential” needs to be developed. All existing dosage forms currently on the list for children would need to be reviewed and ratified as essential, and additional products would need to be reviewed, according to priorities to be established.

Furthermore, the technical expertise necessary to review applications for essential medicines for children requires skills additional to those needed for a review of adult medicines. It needs to take account not only of paediatric clinical medicines, but also of factors such as the different pharmacokinetics of medicines in children of different ages.

In terms of advocacy and promoting access to essential medicines for children there are distinct advantages to initially having a separate process for

determining essential medicines for children, although in the medium-term (3–5 years) it is unlikely to be necessary to maintain a separate system.

According to WHO regulations governing Expert Committees, the mechanism that can be used for this purpose is the establishment of a subcommittee of the Expert Committee with specific terms of reference. Formal subcommittees of Expert Committees need to be recommended by the relevant Expert Committee and approved by the Executive Board or World Health Assembly (Regulations for Expert Advisory Panels and Committees, 4.10 and 4.11). The rules governing the operation of subcommittees are the same as those governing the operation of the parent Expert Committee. Through UNITAID, the International Drug Purchase Facility being established with funding from Brazil, France, Chile, Norway and the United Kingdom, resources are now available to allow the first meeting of such a subcommittee to take place in July 2007. UNITAID is being established as an innovative funding mechanism to accelerate access to high-quality drugs and diagnostics for HIV/AIDS, malaria and TB in countries with a high burden of disease.

The Secretariat proposed that the first meeting in July 2007 would be followed by a second meeting in mid-2008, to complete development of an Essential Medicines List for Children. It is unlikely that the subcommittee would need to continue to exist after the second meeting. It could therefore report to the 2009 regular meeting of the Expert Committee, and make proposals on how the specialized functions necessary to maintain the Essential Medicines List for Children could be carried forward. The subcommittee could be dissolved if the work were complete.

The Expert Committee considered the proposal to establish a subcommittee on the Selection and Use of Essential Medicines for Children, with the following terms of reference:

- develop a WHO Model List of Essential Medicines for Children, based on their clinical needs and the burden of disease;
- develop suitability criteria for dosage forms of medicines for children with particular reference to the developing world;
- review the feasibility of manufacturing appropriate formulations for those priority medicines for which none currently exist, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups;
- identify the gaps in clinical research regarding safety and efficacy of essential medicines for children to improve suboptimal prescribing and dosing, and also to facilitate regulatory approval of paediatric formulations; and
- report to the Expert Committee on the Selection and Use of Essential Medicines in 2009.

The Committee noted the comments from the representatives of SIOP and IUPHAR supporting the proposal. It also noted the resolution from the 120th session of the Executive Board, EB120.13, requesting the Director-General and Member States to take action to make available better medicines for children. It therefore decided to recommend to the Director-General and the Executive Board that a subcommittee be established as proposed in the Secretariat documents.

3.3 **Proposal on listing fixed-dose combination products for infectious diseases**

The “Procedure to update and disseminate the WHO Model List of Essential Medicines, Criteria for Selection” was modified in 2005 to include the following statement regarding fixed-dose combination products (FDCs):

“Most essential medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, adherence or in delaying the development of drug resistance in malaria, tuberculosis and HIV/AIDS.”

Given that the agenda for this meeting required consideration of several applications for new FDCs for the three main infectious diseases, the Secretariat sought clarification of the principles on which drug selection should be based, before any individual application is considered.

From a regulatory viewpoint, for FDCs it would also be necessary to demonstrate bioequivalence of the single combined dose unit with the components administered at the same doses separately but concomitantly. These requirements for efficacy of the combination beyond that of the individual drugs and for bioequivalence are relevant to all clinical areas, including infectious diseases.

The Committee noted the report of the 2005 Expert Committee (*1*) which described a number of different scenarios for possible registration of FDC products. It seemed likely that most products to be considered by the Committee would be described according to “Scenario 2” in the specifications i.e.

“the new FDC contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same or the established regimen may involve combinations of single entities and FDCs, for example a single entity finished pharmaceutical product (FPP) combined with an FDC–FPP that contains two actives. In all cases, the established regime has a well characterized safety and efficacy profile, and all the FPPs used in obtaining clinical evidence have been shown to be of good quality.”

Accepting this, the Committee noted that for products fitting this description, this would imply that clinical trials of the FDC would not usually be required; bioequivalence between the FDC and the components could be used to infer clinical efficacy and safety of the combination.

The Committee considered the evidence available to support the proposal that FDCs improve adherence, noting the results from two recent systematic reviews (2, 3) that address the question of whether FDCs have a positive effect on adherence to medication regimens and also the WHO report from a meeting in 2003.¹

These reviews reveal that there have been very few clinical trials that have assessed the relationship between FDCs and adherence to treatment, and those studies that exist have significant methodological flaws. There is therefore limited direct evidence that strongly supports the benefits of use of FDCs. However, the WHO report of 2003 noted that “FDCs/CBCs are very important tools for scaling up treatment for HIV and AIDS, TB and malaria and remain the first choice when they are available. Fixed-dose combinations and co-blistered combinations (CBCs) must be considered as one element in an effort to ensure adherence that also includes supportive counselling, appropriate information and other measures.”

One advantage of FDCs compared to loose combinations is that if one component of a loose combination is missing, resistance is more likely to develop. A disadvantage is that the optimal combinations of components may change rapidly. The Committee recognized the rapid development of the science of therapeutics in the area of infectious disease and that new FDCs may be conceptually appropriate. The Committee recognized that some FDCs could encourage rational prescribing (e.g. because they would avoid use of antagonist compounds together).

The Committee also considered whether or not a decision to list an FDC requires the existence of a prequalified product or whether the Committee wishes to identify FDCs that are clinically desirable, to list them and use this mechanism to encourage reputable manufacturers to produce quality products to recognized specifications.

On balance the Committee decided that it will consider listing some existing FDCs that would be useful to countries that use the list for procurement. However, the Committee also wants to encourage the development of new FDCs and trials comparing these.

¹ *Fixed-dose combinations for HIV/AIDS, tuberculosis, and malaria. Report of a Meeting held 16–18 December 2003, Geneva*, at: <http://www.who.int/medicinedocs>

The Committee decided that co-packaged products for use in combination but not formulated as an FDC, can be assumed to be covered by listing individual components.

Overall, the Committee, having reviewed its current criteria for listing FDCs as essential medicines, decided to retain them unchanged.

3.4 Report from the Advisory Committee on Safety of Medicinal Products

The fourth meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP) took place on 26–27 February 2007. Reports on the safety of medicines proposed for addition to the Model List were provided by members of the Advisory Committee for review by the Expert Committee.

The Committee recognized the usefulness of the reports provided. The Committee noted that it would also be helpful to have:

- summaries of safety data (in contrast to the raw data) that also distinguish between data from areas with rigorous adverse event reporting systems and those from areas with no such reporting systems;
- interpretation of and opinion on the safety data; and
- safety data in advance of the meeting, for experts to review with the application.

The Expert Committee also noted that it would be useful if the ACSoMP could develop a mechanism for collecting and interpreting safety data on currently listed medicines and reporting these data to the Committee on a regular basis. Such a reporting system could be used to promote safe use of medicines by providing early warnings of problems and could contribute to developing a process for the rapid deletion of products for safety reasons. The Safety Committee could also point out gaps in the available safety data.

3.5 Update of dosage forms and strengths for products on the Model List

In 2006, the University of Liverpool, England, carried out a complete review of the web site of the WHO Medicines Library. The Committee noted the detailed report of the review.

During the review, a number of products on the 14th WHO Model List of Essential Medicines were identified for which the dosage form and strength given in the List were not available in a sample of markets. For some products alternative dosage forms and strengths exist in at least one of the markets. Subsequent review of the missing products in additional markets finally led to identification of six medicines that do not appear to be registered products and in addition an important error in the strength of

a medicine. The Secretariat carried out a limited review of the evidence for each and proposed actions for the Committee to consider:

- *aluminium acetate*: proposed for fast-track deletion on the grounds that there was no evidence of benefit;
- *iopanoic acid*: proposed for fast-track deletion on the grounds of only being used as diagnostic agent in an obsolete investigation;
- *neomycin/bacitracin*: proposed for possible deletion on the grounds of limited evidence of benefit and alternatives being available;
- *nifurtimox*: proposal that this medicine should be retained on the grounds of evidence of benefit in the treatment of Chagas disease and that further information be sought about dosage form and strength;
- *propylidone*: proposed for fast-track deletion, on the grounds of being used for an investigation that is now obsolete;
- *triclabendazole*: proposal that this medicine should be retained on the grounds of evidence of benefit in fascioliasis and paragonimiasis and that further information be sought about dosage form and strength;
- *epinephrine*: proposed change in dosing strength from 1 mg to 100 microgram/ml.

The Committee agreed to delete iopanoic acid and propylidone and to change the dose for epinephrine. The Committee noted that these proposed actions had been posted on the meeting web site for 2 months and were also circulated through e-drug, the electronic discussion group, and no comments or objections to the proposed deletions had been received. The Committee proposed to retain aluminium acetate and neomycin/bacitracin as different strengths of products had been identified. However, it was noted that Section 13 of the Model List – Dermatological Medicines – was in need of general review.

The Committee agreed upon the following principles for specifying dosage form and strength, and recommended that the list be revised accordingly.

In general:

- When a product has been in use for some years and there is a traditional means of expressing dose, change would lead to confusion. In such cases no change should be made.
- WHO should follow the guidelines in the *International Pharmacopoeia* as to expression of dose.
- Even if changes to expression of dose are desirable, it is not appropriate for the Essential Medicines Committee to make such changes unilaterally.

Subject to the above, in general:

- The dose of acids and bases should be expressed in terms of the free acid or free base, even if the product is presented as a salt. The salt

form should be indicated in brackets in the form “(present as the [hydrochloride])”.

- When a drug is formulated as a solvate, dose should be expressed in terms of the anhydrous substance.
- The dose of esters should be expressed in terms of the ester. Different esters may have different potencies.
- If:
 - a new product has been formulated to contain a “rounded” dose; and
 - pivotal clinical trials have been conducted with the specified product and
 - one or more major regulatory authorities have approved the product in these terms, or the product is widely available;then the dose should continue to be expressed in this manner even if it does not meet the above criteria.

It was also noted that clarification of dose expression will highlight anomalies on the Model List but the clinical importance of differences may not be so clear.

3.6 Rare diseases proposal

In 2005, the Committee considered the issue of rare diseases as a result of concerns expressed about the possible deletion from the Model List of factor VIII and factor IX and medicines for other rare diseases also known as “orphan diseases”. At that time the Committee suggested that there was a need for WHO to establish a policy advisory group on rare diseases to study this issue. The discussion paper has now been published by Stolk et al. (4) in the *Bulletin of the World Health Organization* with an accompanying editorial (5).

The Committee further considered the option of establishing an advisory group to consider medicines for rare diseases and to agree on selection criteria for medicines for orphan diseases. The alternative proposal is to develop mechanisms to formally incorporate cost-effectiveness analysis as a basis for decision-making for all products.

The technical requirements for cost-effectiveness evaluation of pharmaceuticals at the global level are substantial, and require methodological development. The Committee might need to define “acceptable” cost-effectiveness thresholds, as has emerged from decision-making systems using cost-effectiveness evaluations in Australia and the UK (6). The Committee acknowledged the methodological difficulties related to assessing applications for medicines for rare diseases.

The Committee decided to maintain the current approach for selecting essential medicines including medicines for rare diseases. This is, effectively, maintaining the approach of considering comparative effectiveness, safety,

cost and need, taking overall public health into consideration. WHO is encouraged to develop relevant cost-effectiveness methodologies for the selection of essential medicines for rare diseases.

3.7 Procedure for updating the content of the Interagency Emergency Health Kit

The agencies of the United Nations system and international and nongovernmental organizations are increasingly called upon to respond to large-scale emergencies, many of which pose a serious threat to health. Much of the assistance provided in such situations is in the form of medicines and medical devices (renewable and equipment).

During the 1980s, WHO took up the question of how emergency responses could be facilitated through effective emergency preparedness measures. The aim was to encourage the standardization of medicines and medical supplies needed in emergencies to permit a swift and effective response to the need for medicines and medical devices by providing standard, pre-packed kits that could be kept in readiness to meet priority health needs in emergencies.

The “WHO Emergency Health Kit” was the first such kit when it was launched in 1990. The second kit, “The New Emergency Health Kit 98” was the outcome of the revision and further harmonization by WHO in collaboration with a large number of international and nongovernmental agencies. The third kit, the “Interagency Emergency Health Kit 2006” (IEHK 2006), accommodates emergency care of people with AIDS, the increasing antimicrobial resistance to commonly available antimalarials and antibiotics, injection safety policy, and the experience of agencies using the emergency health kit in the field.

The content of the emergency health kit is based on the health needs of 10 000 people for a period of three months, the acute phase of an emergency. The kit is composed of 10 basic units and one supplementary unit.

Over the years, the number of partners included has risen from two in the early 1980s to more than 10 partners and suppliers in 2006. The kit was last updated by consensus and there were some difficulties and delays in doing so. As a result, the Secretariat has proposed a process to formalize future revisions, including oversight by the Expert Committee after appropriate consultation.

The Committee reviewed the proposal to update the procedures for revising the Emergency Health Kit and, with the following modifications, endorsed the proposal from the Secretariat. The Model List will serve as a basis for including medicines in the IEHK. Therefore, if a medicine already appears on the Model List, a full application will not be required. Supplementary

information on quantities and sources of the medicines may be required. The Committee noted that the IEHK does not currently address the needs of children. The procedures are described in Annex 6.

3.8 Late agenda item on medicines for acute care

The Committee commented on a late agenda item, which proposed identifying medicines used for acute or emergency care. The Secretariat was requested to systematically gather data to create a list of the types of medicines currently used in emergency care and to compare this list with the Model List.

3.9 Report on WHO Model Formulary

The WHO Model Formulary (WMF) was first published in 2002, after the WHO Expert Committee on Selection and Use of Essential Medicines recommended its development in 1995. The original purpose of the Formulary was:

“to provide general information and information on prototype drugs in the Model List of Essential Drugs according to the specifications as shown in the sample drug information sheet overleaf. This information could then be adapted by countries according to their own needs and would be a key element in rational drug use.”

The WMF was updated in 2004, and published as a book, a CD and in an online version. In addition, a manual designed to assist countries to adapt the WMF to national needs was published. Both the 2002 and 2004 editions of the WMF were prepared by the Royal Pharmaceutical Society (RPS) of Great Britain on contract to WHO, and the manual benefited from considerable input from the Society as well. The preparation for the 2006 edition did not start until October 2005. There were numerous subsequent delays in the process and the 2006 edition was not published on the web site until January 2007.

The Committee noted the review of the need for the formulary carried out by the Medicines Policy and Standards department of WHO. From the relatively limited feedback, it would seem that the WMF is used in a variety of ways for many different purposes, including as a reference in clinical practice or as a policy tool. Importantly, the print version was reported to be used by more respondents than the electronic version. The WMF is also used by UNICEF as the source of drug information related to the products it supplies, is included (in printed form) as a reference book in emergency health kits, and has been adapted by several countries and organizations. The WMF can serve as a source document for a national formulary. This could be achieved by providing an electronic document that can be edited and adapted.

The Committee considered the report from the Secretariat, the response from the RPS and comments by expert reviewers. Overall, it is apparent that there is a need for the Model Formulary, as it is an important source of drug information in settings with limited resources. The printed version is essential. However, the Committee agreed that the current production process was not satisfactory and therefore supported the proposal by the Secretariat to consider other ways of generating and maintaining the text. Possible options discussed were:

- full technical review of monographs only for newly added medicines;
- less frequent production of the formulary;
- development of mechanisms for dealing with different electronic formats;
- local production of print copies, or invitation of competitive bids for production.

The Committee recommended a pilot project to produce national formularies derived from an electronic version of the WMF and sufficient funding to accomplish this goal.

The Committee also noted the report on the technical update of the Essential Medicines Library.

3.10 **Report on Drug Bulletin manual**

In 2005, WHO and the International Society of Drug Bulletins (ISDB) published a manual entitled “*Starting or strengthening a drug information bulletin*”. The authors came from both developed and developing countries. The manual provides detailed information on drug bulletins, planning, the editorial process, reviewing a new drug, design and production of the bulletin, dissemination, evaluating quality and usefulness of the product, and partnership and collaboration. The first 100 copies of the manual were produced with the financial support of the European Union. ISDB objected to this arrangement and the manual is now only available electronically on the WHO and ISDB web sites.

The Committee noted the report on the manual, regretted the lack of adequate publication and dissemination and endorsed the proposal that the manual be included on the CD-ROM with the WHO Model Formulary.

3.11 **Review of proposal regarding critically important antibiotics**

In 2005, the Committee considered a report from a working group consultation that took place in February 2005 in Canberra, Australia, with the remit of developing the concept of critically important antibiotics. This involved defining criteria for classifying antibiotics according to their level of importance for use in humans and then classifying all antibiotics according

to these criteria. It is envisaged that recommendations will be made that antibiotics deemed critically important should not be used in non-humans. The results of the consultation are reported in the document *Critically important antibacterial agents for human medicine for risk management strategies of non-human use*. The Committee noted the value of this report and recognized its importance for human health. The Committee endorsed the concept of identifying antibiotics that should be reserved for use only in humans and supports WHO taking the initiative to identify these antibiotics. It was noted that the labels of “critically” and “highly” important could be confusing and the full definitions of these categories could be used instead.

In response to the specific questions put to the Committee, the following comments were made:

- How does the concept of critically important antibiotics fit in with that of essential antibiotics? If the two concepts are different, how can we ensure there is a clear understanding of the two concepts by Member States and other interested parties? This will necessarily require consideration of the criteria for defining essential antibiotics and critically important antibiotics.

The Committee noted that the report states that this list of antibiotics is different to the antibiotics on the Model List.

- What process should be used for taking forward the issue of critically important antibiotics that are also essential antibiotics? Should a committee of experts sit regularly to advise WHO on how to preserve the effectiveness of these drugs taking into consideration human use as well as animal use? What should be its structure, procedures and membership?

The Committee recommends that WHO establish an advisory group that will meet regularly to produce and update the list of antibiotics that are permissible or not for non-human use. This should be an interagency structure involving the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).

- How should antibiotics that are deemed essential (i.e. included in the Model List of Essential Medicines), but not critically important be dealt with? Should specific recommendations be made with regard to their use in animals?

The Committee urges the newly constituted Advisory Group to consider these questions.

3.12 **Advice on draft resolution on rational use of medicines**

In 2005, the 58th World Health Assembly discussed *Rational use of medicines by prescribers and patients (7)* in the context of the threat posed to global

health security by antimicrobial resistance and adopted resolution WHA58.27 on *Improving the containment of antimicrobial resistance*. At that time many Member States underlined the need for more to be done to rectify the serious global problem of irrational use of medicines. Thus, the Executive Board discussed *Rational use of medicines: progress in implementing the WHO Medicines Strategy (8)* at its 118th session in May 2006 and again at its 120th session in January 2007. EB resolution 120.R12 was adopted for further consideration at the World Health Assembly in May 2007.

The Committee considered the resolution and the Secretariat's report, together with the other referenced documents and the proposed plan of implementation, and considered the following questions:

- Does the present EB resolution to be submitted to the WHA in May 2007 sufficiently address the needs outlined in the Secretariat's report? If not, what is missing and what needs to be added?

The Committee felt that the resolution provided a good starting point for implementing the proposed global programme to promote rational drug use.

- Should a steering committee be established to oversee implementation of a global programme to promote rational use of medicines as envisioned in the present Secretariat's report and draft resolution? If so:
 - Should it be a subcommittee of the Expert Committee on Selection and Use of Essential Medicines?
 - What should be its membership?
 - How often should it meet?

The Committee endorsed the formation of an Advisory Group which could draw members from WHO panels or Expert Committees, including, for example, the Essential Medicines Committee. The Committee recommended that the Advisory Group include technical advisers and that the Secretariat choose the specific structure for the group. Members of the Essential Medicines Committee expressed interest in being part of the Advisory Group.

- What major steps in addition to those suggested above should be undertaken to implement the resolution and establish a global programme to promote rational use of medicines that includes the setting up of national programmes as recommended by the second International Conference on Improving Use of Medicines (ICIUM) 2004?

A first step would be to form a multidisciplinary Advisory Group with appropriate membership, including representation from the WHO regions.

The Committee acknowledged the importance of WHO taking a leadership role in promoting rational drug use worldwide. The Model List of Essential Medicines is a mechanism for promoting rational drug use and the Committee supports additional efforts to promote rational use.

The Committee recognized the lack of coordination within rational use programmes at the country level and the difficulty in gaining access to local data on medicine use. The proposed resolution could assist Member States in taking advantage of programmes that WHO has already set up. WHO could expand its network of relevant people in each country who are active in promoting rational use of medicines. The Committee raised concerns about the diffuse nature of the specific programme proposed, and thus supported the idea of an Advisory Group to guide implementation of the programme.

The Committee noted that the issue of irrational use of medicines is global and that a global approach coordinated by WHO is essential. The Committee, therefore, strongly endorses Resolution EB120.R12 “Rational Use of Medicines” and is eager to see WHO implement more vigorous leadership and evidence-based advocacy of rational use of medicines.

4. **Changes made in revising the Model List by section: medicines for all populations**

4.1 **Section 2: addition of prolonged-release morphine**

An application for inclusion of morphine (as sulfate) 10, 30 and 60 mg modified-release tablets was submitted by the Cochrane Pain, Palliative and Supportive Care Group, with support from the International Association for Hospice and Palliative Care.

Expert reviews of the application were prepared by: Dr Liliana De Lima¹ and Dr Alar Irs.² Comments in support of the application were received from Dr Lembit Rägo, Coordinator, QSM/WHO. Additional supporting statements were received from Médecins Sans Frontières.

The Committee noted that the application provided a thorough review of the evidence regarding the effectiveness and safety of the prolonged-release morphine formulation for management of chronic pain, based on systematic review (9) of its use in patients with chronic cancer pain. The public health need for inclusion of a new formulation of morphine on the Model List was fully substantiated. The current problems of inadequate access to morphine for use in palliative care in many countries were also described. As noted by the expert reviewers, the clinical evidence showed that the modified-release formulation and immediate-release formulations are equivalent for pain management in chronically ill (cancer) patients. Quantitative estimates of the analgesic effect were not calculated by the authors of the review

¹ Dr Liliana de Lima, International Association for Hospice and Palliative Care, Houston, TX, USA, is a Member of the Expert Committee.

² Dr Alar Irs, State Agency of Medicines, University of Tartu, Tartu, Estonia, is a Member of the Expert Committee.

owing to the insufficiency of comparable data for a meta-analysis to be undertaken. The Committee noted that modified- and immediate-release morphine preparations share a common adverse effects profile (nausea, vomiting, constipation, drowsiness and confusion).

The Committee also noted that prolonged-release dosage forms may not be interchangeable because the nature of release modification (rate and mechanism) may differ, and owing to the effect of patient variables (e.g. altered gastrointestinal motility or food intake) may not be the same for all products.

Generic prolonged-release preparations of morphine are available worldwide and its inclusion on the Model List may stimulate production of generics.

Overall the evidence provided in the application supports the public health need, effectiveness and safety of prolonged-release morphine formulation. The Committee therefore recommended that morphine sulfate 10-, 30- and 60-mg prolonged-release tablets be added to the Model List. These dosages are not applicable for paediatric patients and will be reviewed at the meeting of the Subcommittee on Children's Medicines.

4.2 **Section 6.1: deletion of levamisole as anthelmintic**

Expert reviews of the application for the deletion of levamisole as an anthelmintic were prepared by: Dr Eva M.A. Ombaka¹ and Dr Usha Gupta.² Additional supporting statements were received from The Center for Drug Reevaluation, SFDA, People's Republic of China. After review, the Committee recommended that levamisole be retained on the Model List.

In 2005, the Advisory Committee on Safety of Medicinal Products reviewed adverse events associated with levamisole. This review was prompted by a report from China which suggested that levamisole was associated with an encephalitis-like syndrome, levamisole-induced demyelinating encephalopathy. The Chinese literature contains 543 published reports of cases of this event. The 2005 meeting of the Advisory Committee proposed that the product should be deleted from the Model List given that it had been withdrawn from the Chinese national formulary, and then reviewed this recommendation together with the adverse event data from China at its most recent meeting in 2007.

The main ground for the request for deletion was the toxicity of the medicine. The Committee noted the argument made that there are safer and more effective alternative anthelmintics, but no comparison of effectiveness was

¹ Dr Eva M.A. Ombaka is Coordinator of the Ecumenical Pharmaceutical Network.

² Dr Usha Gupta, Delhi Society for Promotion of Rational Use of Drugs, Delhi Government Dispensary, New Delhi, India, is a Member of the Expert Committee.

provided. In addition to the Chinese literature, a search of other scientific publications identified a further possible 4–6 cases of encephalopathy, but only in the context of cancer chemotherapy. Doses used to treat cancer patients are higher than doses for use as an anthelmintic and the duration of treatment is longer. No cases of encephalopathy were found in the Uppsala Monitoring Centre database.

Noteworthy in the Chinese data is the apparent concentration of cases in one region where levamisole was being sold by “folk doctors”; 75.5% of cases were apparently reported as having occurred in patients who had obtained the drug from this source. This may call into question the quality and content of the product used.

The Department of Control of Neglected Tropical Diseases opposed the deletion of levamisole for this indication. It noted that levamisole is effective, and may also be of value when used in combination with mebendazole in delaying the development of benzimidazole resistance, as noted in the recent treatment guidelines (10) which continue to recommend levamisole, for *treatment* of soil-transmitted helminthiasis but not in preventive programmes. In addition, there are few anthelmintics currently on the list or in development.

The Committee noted that the evidence in the application is from one country. Although the reaction is recognized in the context of cancer chemotherapy, it does not seem to have been reported in the context of use as an anthelmintic from other settings. The assessment was made more difficult by the absence of a review of comparative effectiveness.

The Committee therefore decided to retain levamisole on the Model List as an anthelmintic but will review it again in 2009. To inform this review, the Committee recommended that the ASCoMP gather additional information on the safety of levamisole at the doses and duration for which it is used as an anthelmintic. The Committee also anticipates a review of comparative effectiveness.

4.3 **Section 6.2.1: Beta lactam: addition of cefazolin/cefalexin**

Expert reviews of the application were prepared by: Dr A. Helali¹ and Dr Youping Li.²

In 2005, the Expert Committee considered the priority review on cephalosporins by the ISDB and requested that a formal application for the first-generation cephalosporins (cefazolin and cefalexin) be submitted for the 2007 meeting.

¹ Dr Abdelkader Helali, Centre National de Pharmacovigilance et Matériovigilance, Ministère de la Santé et de la Population, Alger, Algeria, is a Member of the Expert Committee.

² Dr Youping Li, Chinese Cochrane Centre, West China Hospital, Sichuan University, Chengdu, People's Republic of China, is a Member of the Expert Committee.

The application was therefore commissioned by the Department of Medicines Policy and Standards. The proposal is to list cefazolin (injectable, 1 g/vial) for surgery prophylaxis and cefalexin (capsules, 250 mg/capsule and 500 mg/capsule, and syrup (powder to be reconstituted with water – 125 mg/5 ml and 250 mg/5 ml) for treatment of skin infections which are a major public health problem especially in children and in developing countries. Both cefazolin and cefalexin are available as generic preparations.

Cefazolin

The application presented a summary of the evidence for the effectiveness of cefazolin for surgical prophylaxis. As noted by the expert reviewers, there is high-quality clinical evidence, based on a systematic review (11), that shows that cefazolin for surgical prophylaxis in women undergoing caesarean section is as effective as ampicillin (relative risk (RR) 1.24, 95% confidence interval (CI): 0.84 –1.83) or second- or third-generation cephalosporins (RR 1.17, 95% CI: 0.97– 1.40) in preventing endometritis. Cefazolin has also been shown to be effective in preventing wound infection in patients undergoing peripheral arterial reconstruction (12).

On balance, as the evidence provided in the application supported the public health need, effectiveness and safety of cefazolin, the Committee recommended that cefazolin (injectable, 1 gm/vial) be added to the core list, with a note “for use as surgical prophylaxis”.

Cefalexin

Cefalexin has been shown to be effective in treating skin and soft tissue infections in multiple trials in which it was compared with erythromycin, azithromycin, other third-generation cephalosporins and dicloxacillin (13), although the evidence is comparatively limited. The evidence from these trials has not been the subject of a Cochrane systematic review. The application refers to one of the studies which demonstrated equal efficacy and safety of cefalexin compared to moxifloxacin in 401 adults with uncomplicated skin infections (14), although this may not be relevant as moxifloxacin is not on the Model List. A Cochrane review of interventions for impetigo (Koning, 2003) (13) was based on 57 trials involving 3533 participants, which compared 20 different oral medicines, including cefalexin, and 18 different topical treatments. The trials were in children and adults. Settings and countries were not specified. The results did not show significant differences in cure rates between oral antibiotics or topical and oral antibiotics. Cefalexin is generally well tolerated.

In making its decision, the Committee noted that:

- Cefalexin has been shown to be effective in treating skin and soft tissue infections in multiple trials and it is commonly used to treat staphylococcal infections.

- Addition of a narrow-spectrum antimicrobial to the list could promote rational prescribing.
- It can be an inexpensive alternative for patients who are allergic to penicillins.
- Cefalexin in liquid form may be more acceptable to children than penicillin preparations.

However, the Committee also recognized that cefalexin, in particular, is widely used for inappropriate treatment of viral infections of the upper respiratory tract in children in many countries.

On balance, the Committee decided in view of the lower quality of the evidence for the comparative effectiveness of cefalexin, and the overall concerns about inappropriate use of antibiotics, not to add cefalexin to the Model List at this time.

4.4 **Section 6.2.4: Antituberculosis medicines**

4.4.1 ***Addition of rifampicin + isoniazid + ethambutol***

Fixed-dose combinations (FDCs) of anti-tuberculosis medicines (isoniazid + ethambutol tablet, rifampicin + isoniazid tablet, several strengths; rifampicin + isoniazid + pyrazinamide tablet, several strengths, including paediatric; and rifampicin + isoniazid + pyrazinamide + ethambutol tablet) are included on the Model List to improve adherence and are recommended by the WHO guidelines (15).

An application for inclusion of a 3-FDC rifampicin 150/isoniazid 75/ethambutol 275 mg (RHE) was received from the STOP-TB Partnership.

Expert reviews of the application were prepared by: Dr Alar Irs¹ and Dr Youping Li.²

The Committee noted that there were no published trials that had used either the proposed FDC or the components in loose combination. One small bioequivalence study was presented. The major justification for the product was as an additional fixed-dose formulation for treatment of TB diagnostic category II as recommended in the WHO treatment guidelines (15). The clinical role of the product is in the continuation phase of treatment for category II patients, after the first two months, when pyrazinamide is no longer effective. The doses of the components proposed in this combination are consistent with current dosing guidelines based on weight of patients (using four weight bands) and also with the quantities in the four-component

¹ Dr Alar Irs, State Agency of Medicines, University of Tartu, Tartu, Estonia, is a Member of the Expert Committee.

² Dr Youping Li, Chinese Cochrane Centre, West China Hospital, Sichuan University, Chengdu, People's Republic of China, is a Member of the Expert Committee.

FDC already on the Model List. Evidence for the safety of the three-component FDC is based on the use of the four products in combination.

The Committee noted that the product is available through one supplier, but that there are no stringent regulatory authority approvals. Adding the product to the Model List might therefore be a stimulus to making available additional quality products. The product is listed on the Prequalification Programme expression of interest (EOI) and as of the last public report, no triple FDCs were listed as prequalified.

The Committee considered its agreed criteria for FDCs (see Section 3). This combination is recommended in the relevant WHO treatment guidelines for category II TB patients, but there are only uncertain estimates of the size of this subpopulation. Although the Committee was concerned by the absence of clinical trial data, on the basis of pharmacological and microbiological evidence, it decided to include rifampicin 150 mg/isoniazid 75 mg/ethambutol 275 mg on the core list.

4.4.2 **Section 6.2.4: Review of quinolones for multidrug-resistant TB**

Expert reviews of the application were prepared by: Dr Rohini Fernandopulle¹ and Dr Marcus M. Reidenberg.² Comments in support of the application were received from Dr Mario Raviglione, Director, Stop TB (STB).

Ciprofloxacin 250 mg and 500 mg, levofloxacin 250 mg and 500 mg, ofloxacin 250 mg and 400 mg tablets are included in the 14th Model List as complementary medicines for second-line treatment for multidrug-resistant TB, to be used in specialized centres adhering to WHO standards for TB control. Levofloxacin is the S-isomer (the active isomer) of the racemic mixture ofloxacin. These medicines were marked for review at the meeting of the 15th Expert Committee.

A review was commissioned by Stop TB to revise the listing for fluoroquinolones. The review concluded that the single fluoroquinolone to be nominated on the list should be levofloxacin, but without a square box. The review argued that as levofloxacin is the S-isomer of ofloxacin, there is no need to list both medicines and therefore a square box is not needed. Ciprofloxacin was not considered an appropriate alternative for routine use. The Committee noted that there was a very limited evidence base upon which to assess the relative clinical effectiveness of ciprofloxacin, ofloxacin and levofloxacin. While there are some data to support lower minimum

¹ Dr Rohini Fernandopulle, Department of Pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka, is a Member of the Expert Committee.

² Dr Marcus M. Reidenberg, Division of Clinical Pharmacology, Weill Medical College of Cornell University, New York, NY, USA, is a Member of the Expert Committee.

inhibitory concentrations (MICs) and higher peak concentration (C_{\max})/MIC with levofloxacin, it is difficult to translate this evidence into clinical practice recommendations. There is some evidence from observational studies (retrospective analyses of a series of treated patients) to suggest that levofloxacin is superior to ofloxacin (16).

However, it is difficult to assess the influence of trends over time in prescribing, doses used and other clinical factors in the treatment decisions on these observations. The recommendation not to use ciprofloxacin as an equivalent first-line drug substitute is based on the observations from a small number of trials where ciprofloxacin substituted into first-line regimens in drug-sensitive TB resulted in an increased risk of relapse and prolonged time to cure (17).

No data were presented on the cost-effectiveness of the fluoroquinolones nor were comparative price data included in the review. However, International Drug Price Indicator estimates suggest that levofloxacin could be a substantially more expensive treatment option.

Given the absence of any randomized controlled trials comparing the relative effectiveness of the three fluoroquinolones and of any evidence of substantially different adverse event profiles for these drugs, the Committee agreed that there were no compelling grounds on which to select one agent over the others for the treatment of multidrug-resistant TB. Comparative studies are needed. Current studies are examining the roles of moxifloxacin and gatifloxacin in TB, so further trial data on these three fluoroquinolones are unlikely to become available.

Given some evidence of the higher price of levofloxacin than ofloxacin and ciprofloxacin and recognizing the concerns of STB about the costs of medicines if only levofloxacin is listed, the Committee decided to include ofloxacin on the complementary list. Rather than adding a square box, the Committee decided to add a footnote noting that the alternative is levofloxacin based on availability, cost and programme considerations.

4.5 Section 6.4.2: Antiretrovirals

4.5.1 **Section 6.4.2.1: Nucleoside reverse transcriptase inhibitors: addition of emtricitabine**

Expert reviews of the application were prepared by: Mr Andy Gray¹ and Dr Abdelkader Helali. Dr Albert Figueras² withdrew from the discussion of this and all other proposals on HIV medicines.

¹ Mr Andy Gray, Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa, participated as Temporary Adviser in the Expert Committee.

² Dr Albert Figueras, Fundació Institut Català de Farmacologia, Servei de Farmacologia Clínica, Hospital Vall d'Hebron, Barcelona, Spain, participated as Temporary Adviser to the Expert Committee.

In 2005, the Expert Committee considered an application from the manufacturer for inclusion of emtricitabine as an additional nucleoside reverse transcriptase inhibitor (NRTI). At that time, the application was based mainly on unpublished studies and the Committee deferred its decision on the product until the data were publicly available. The application has since been resubmitted.

Emtricitabine is listed in the current WHO guidelines for the treatment of adults and children (18, 19) as one option for first-line combination treatment as part of the NRTI backbone, and as an alternative to lamivudine (3TC). According to the guidelines, “FTC [emtricitabine] is an equivalent alternative to 3TC as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus and has the same resistance profile.”

The application provided an updated summary of the evidence, including seven trials in adults and two in children. The majority of the trials are those submitted for regulatory purposes, but most have now been published as peer reviewed papers. The trials were limited to developed countries and experience of the use of emtricitabine in developing countries remains limited. In summary, the trials show that:

- Emtricitabine can be used in both treatment-naive and experienced patients.
- The once daily treatment regimen is at least as effective as dosing with other medicines, as measured by effect on standard viral load and CD4 outcomes.
- Emtricitabine has been used in combination with different medicines, as outlined in the WHO treatment guidelines, and therefore can be used in a variety of different combination treatments.
- The effect on viral load is durable.
- The product can be used in children from 3 months of age.
- The safety profile of the product, particularly with regard to hyperpigmentation, is acceptable.

There are no data on use of emtricitabine in pregnancy.

A summary of accumulated safety data to date was also provided. The majority of reported use is in developed countries. Adverse reactions to emtricitabine are similar to those reported for other medicines in the class.

The Committee considered the question of interchangeability with lamivudine, based on clinical trials directly comparing the two medicines. From the evidence provided, there did not appear to be any clinically significant difference in effectiveness.

No evidence of cost-effectiveness was provided. The Committee noted that there is a proposal from the current manufacturer for differential pricing for emtricitabine and tenofovir FDC, but not for emtricitabine alone.

The Committee concluded that there is sufficient evidence that emtricitabine is effective for treating HIV when used in combination regimens although little of this information comes from resource-poor settings. The safety profile is similar to that of other medicines in the class. Although in practical terms it seems to be used as an alternative to lamivudine, there is insufficient evidence that it is in fact completely interchangeable and therefore listing it by reference to lamivudine with a square box could not be justified. The major advantage of adding emtricitabine to the Model List would appear to be in promoting availability and access to an additional treatment option, as well as offering an alternative to other NRTIs. The Committee therefore added emtricitabine capsule and liquid formulation to the core Model List with a note that it is clinically interchangeable with lamivudine.

4.5.2 **Section 6.4.2.1: NRTI: addition of tenofovir disoproxil fumarate**

Expert reviews of the application were prepared by: Mr Andy Gray and Dr Abdelkader Helali. A comment from Médecins Sans Frontières on the application was noted.

In 2002, the following NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. In 2005, the Expert Committee considered an application from the manufacturer for tenofovir (TDF) as an additional NRTI. At that time the application was based mainly on unpublished studies and the Committee deferred a decision on the product until the data were publicly available. The application has since been resubmitted. Tenofovir is listed in current WHO treatment guidelines for adults and children (18, 19) as one option for first-line combination treatment as part of the NRTI backbone, and as an alternative to abacavir (ABC).

The application provides an updated summary of the evidence, but as noted by the Committee, did not adequately cover all published literature. Some of the supporting evidence is still in the form of conference proceedings and abstracts. The trials presented are restricted to phase III clinical trials comparing TDF to stavudine, or TDF plus TFC to zidovudine/lamivudine FDC or trials with TDF as an add-on treatment in patients with virological failure. The main evidence in the application consists of data from four key regulatory trials. There are ongoing trials in the African region and also in children, but there is as yet no approval for use of TDF in populations younger than 18 years of age.

The application provided an updated review of safety information, dated October 2005. The concerns noted by the Committee in 2005 were the potential for renal toxicity, interactions, lactic acidosis, bone problems and liver problems. Although the supplement to the application provides lists of references that are related to these problems, there was no synthesis or overview of the information provided. The expert review prepared for the

Committee summarized the information in the references, and notes that several other relevant publications have not been considered. Overall, renal problems with tenofovir appear to be real but rare and the uncertainty is therefore the level of monitoring that would be required. Changes in bone density do not appear to be clinically relevant and may be reversible. The data on interactions is based on the product information document and may or may not be sufficient for global use. Lactic acidosis and lipodystrophy may be less of a problem with tenofovir than other currently available antiretrovirals (ARVs), especially stavudine.

In summary, tenofovir has been found to be effective in terms of effect on standard end-points such as viral load measures, for the treatment of HIV-infected adults, when used in combination with other ARVs. The safety profile is now better characterized than when it was considered in 2005, and considerable data are in the public domain. It is not yet approved for use in children. There are ongoing trials of its use in resource-poor settings. The Committee recommended adding tenofovir to the core Model List and noted that the monitoring requirements for this medicine are no different to those for other ARVs.

4.5.3 **Section 6.4.2: Antiretrovirals**

Section 6.4.2.2: Non-nucleoside reverse transcriptase inhibitors: addition of new strength of efavirenz

Supporting statements for the addition of a new strength of efavirenz were received from Médecins Sans Frontières.

Efavirenz was added to the core Model List in 2002 as capsule, 50 mg, 100 mg and 200 mg and oral solution 150 mg/5 ml, when the Expert Committee added the section for non-nucleoside reverse transcriptase inhibitors to the Model List with a recommendation to use these medicines in addition to dual nucleoside core combinations as a third agent. An application for inclusion of a new dosage form of efavirenz, a 600-mg tablet, has now been submitted by Merck Sharp & Dohme Interpharma, La Celle Saint Cloud, France.

The major advantage of the proposed new dosage form is that it can be given once daily, with a resultant reduction of pill burden and a presumed increase in adherence. The application presented results from three studies (20, 21, 22) to support this claim: two controlled trials and one small prospective cohort study. These studies showed that when used as part of different combination treatment regimens, efavirenz once daily was at least no worse than comparators (indinavir, nelfinavir) in terms of its effects on viral load. The benefits of once daily dosing on adherence were poorly substantiated as it was only measured in the cohort study.

In addition, a Cochrane review (23), not included in the application, provides further evidence of the relative effectiveness and safety of efavirenz in combination treatment regimens, in comparison with nevirapine. Efavirenz is contraindicated in pregnancy and it is not approved for use in children under the age of 3 years. The Committee noted that when using the 600-mg form, safety considerations became important in patients whose body weight was less than 40 kg.

Generic preparations of efavirenz are not presently available; the current cost is regulated by the manufacturer according to the prevalence of HIV in adults. Overall, the evidence provided in the application supports the need for the new dosage form. The Committee therefore recommended that efavirenz 600-mg tablet be added to the Model List for the first-line therapy of patients with HIV as part of combination treatment regimens as recommended in the WHO treatment guidelines for HIV.

Section 6.4.2.3: Protease inhibitors

The Committee noted advice from the WHO Department of HIV/AIDS that the evidence for, and experience of use of protease inhibitors is rapidly evolving and new medicines in this class are becoming available. In addition, the dosage form and strength of lopinavir and ritonavir will need to reflect developments in formulation to make heat-stable products. It is anticipated that an application for a heat-stable tablet formulation containing 200/50 mg lopinavir + ritonavir will be submitted for the next meeting. Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combinations as a pharmacological booster, and not as an antiretroviral in its own right.

Therefore, the Committee recommended that the WHO Department of HIV/AIDS conduct an urgent review of protease inhibitors in section 6.4.2.3. Ideally, this review should be conducted according to any new procedures that are developed for updating the list between meetings as the situation regarding protease inhibitors has highlighted the need for capacity for urgent updates of the Model List.

4.5.4 *Fixed-dose combinations of antiretrovirals*

The HIV/AIDS Department of WHO provided an introduction to and overview of the programmatic aspects of use of FDC antiretrovirals. Based on the 2006 WHO treatment guidelines, a list of preferred combinations was presented, which the Committee then considered in its review of all of the proposals for FDCs for HIV.

4.5.4.1 Addition of lamivudine/zidovudine

In 2002, NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. At that time, an application for the combination product containing zidovudine 300 mg and lamivudine 150 mg was also presented, but the decision was to list only single components and to have a note in the Model List about FDC products.

Zidovudine and lamivudine are both listed in the WHO treatment guidelines for adults and children (18, 24) as one option for the NRTI backbone for first-line combination treatment, with either nevirapine or efavirenz as the NNRTI. Given as the combination, the dose is one FDC tablet twice daily with either nevirapine or efavirenz.

Expert reviews of the application were prepared by: Dr Marcus M. Reidenberg. Additional statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application is an update of the review presented in 2002. It is stated in the application that “in compiling the application, it was recognized that there are large numbers of commercial products containing this particular combination, some of which have been subject to rigorous regulatory assessment while others have not.” The application therefore proposes that adequately conducted trials of an FDC or trials involving the components concomitantly administered should be regarded as supportive evidence, i.e. studies that are indicative but not conclusive. The application also points out that if an individual product has been subject to stringent regulatory authority approval, bioequivalence between the FDC and the components can be accepted. Advantages of this two-drug FDC are:

- ease of storage, procurement and distribution; and
- harmonization of prevention of mother-to-child transmission.

This application cites two systematic reviews (25, 26) as the main source of evidence to support the use of the FDC containing zidovudine and lamivudine. It is not clear which of the trials actually used FDCs. Some of the trials are the early comparisons of double versus monotherapy that became the basis of the general recommendation to use combinations of three or more antiretrovirals, which is now accepted as standard. The application notes that AZT/3TC should not be used alone in treatment, but must be used in combination.

With respect to the impact of the FDC on adherence, the application describes two studies, one cohort study (Legoretta et al., 2005) (27) and one randomized controlled trial (RCT) (Enron et al.) (28) that compared adherence in patients who used FDCs containing AZT/3TC with adherence in those who used the individual components. The results of both studies

suggest better adherence in patients using the FDCs, including when used as part of triple combination treatment regimens.

The evidence for comparative safety combines the information on adverse events for the individual components with that on drop-out rates in the clinical trials. There do not appear to be any safety concerns that specifically relate to the use of the FDC. This combination has been used in a variety of settings as part of the roll-out of ARVs and a number of high-quality products are available.

The Committee noted that the unit price and average cost of treatment with AZT/3TC varies enormously. Overall, this combination, one of several proposed in the WHO treatment guidelines, is a preferred combination for first-line treatment, as one of the NRTI backbones. The combination can be used in most subpopulations of HIV patients, including pregnant women and children. Several products of adequate quality exist, containing appropriate doses of the components, and there have been clinical studies using the components of the FDC at the same doses, including two studies that show that its use leads to enhanced adherence, with no worse side-effects. There is also substantial experience of use of this product in resource-poor settings.

The Committee therefore recommended that the FDC should be added to the Model List.

4.5.4.2 **Addition of lamivudine/zidovudine/nevirapine**

In 2002, NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. As noted above, the role of FDCs in scale-up of treatment has become critical and the Department of HIV/AIDS, WHO, has proposed that an FDC product containing zidovudine, lamivudine and nevirapine be included on the Model List.

All three components are listed in the WHO treatment guidelines for adults and children (18, 24) as one option for first-line combination treatment. Given as the combination, the dose is one FDC tablet twice daily.

Expert reviews of the application were prepared by: Dr Marcus M. Reidenberg. Additional statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application is based on a trial of the components given individually. Products of assured quality, including three approved by the WHO Prequalification Programme exist. One observational study (29) evaluated FDC products in general, but it is not possible to separate results for AZT/3TC/NEV.

The five RCTs (30–34) using the components are comprehensively summarized in the application. The results of these trials show that:

- AZT/3TC/NEV is effective in treating HIV and equivalent to 3TC/stavudine/nevirapine.
- AZT/3TC/NEV may be superior to AZT/3TC/nelfinavir in terms of effect on viral load, and possibly health-related quality of life, but seems equivalent in terms of effect on immune recovery.
- AZT/3TC/NEV appears to be equivalent to AZT/3TC/abacavir in terms of effect on viral suppression.

Although AZT/3TC/NEV has been used in a number of countries, there is little information on total exposure. Safety data from the randomized trials are consistent with the known adverse effect profile of the three medicines. Lipodystrophy, rash and anaemia are well-characterized as adverse reactions. The Committee noted that this combination seems to be better tolerated than the stavudine-containing triple FDC and can be used in all relevant populations. No additional information on adherence with this FDC was found.

Overall, this combination is one of several proposed in the WHO treatment guidelines, and is a preferred combination for first-line treatment as it can be used in most subpopulations of HIV patients, including pregnant women and children. Several products of adequate quality exist, containing appropriate doses of the components and there are clinical studies using the components of the FDC at the same doses and one study using this FDC. There is substantial experience of use of this product in resource-poor settings. The Committee therefore recommended that the FDC containing zidovudine, lamivudine and nevirapine should be added to the Model List.

4.5.4.3 Addition of lamivudine/stavudine/nevirapine

In 2002, NRTIs were added to the core Model List: abacavir, didanosine, lamivudine, stavudine and zidovudine. As part of the general proposal on FDCs, the Department of HIV/AIDS, WHO, has proposed that two FDC products containing stavudine, lamivudine and nevirapine be included on the Model List. All three are listed in the WHO treatment guidelines for adults and children (18, 24) as one option for first-line combination treatment. Given as the combination, the dose is one FDC tablet twice daily. The strengths proposed are:

- stavudine 30 mg, lamivudine 150 mg, nevirapine 200 mg for patients under 60 kg;
- stavudine 40 mg, lamivudine 150 mg, nevirapine 200 mg (d4T/3TC/NEV) for patients over 60 kg.

Both products are available from multiple suppliers, including at least two prequalified products.

Expert reviews of the application were prepared by: Dr Marcus M. Reidenberg. Additional supporting statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application is based on trials of the components given individually. In addition, there have been several large observational studies (29, 35) using the FDC product that confirm its effectiveness and safety in a variety of settings, including in resource-poor countries. As noted in the application:

“Changes to viral load measures and CD4 counts are similar to what have been seen in randomized trials and cohort studies performed in developed countries, but clinical event rates and in particular mortality have been higher in the resource-poor settings. This suggests that patients are commencing treatment at a more advanced stage in their illness and co-morbidities, in particular opportunistic and intercurrent infections, are more frequent at baseline. Also, diagnostic and treatment facilities are lacking. The data reviewed here, and the comments of the researchers, indicate that these factors are the most important determinants of the poorer clinical outcomes, rather than poor adherence, viral resistance or inferior quality of the drugs themselves.”

Comparative safety is comprehensively described. As noted, d4T is the NRTI most commonly associated with lactic acidosis, lipoatrophy and peripheral neuropathy and therefore countries should be planning to move away from treatment regimens that include it. However, treatment options that include d4T are currently the most readily available so appropriate monitoring for short- and long-term toxicities is required.

As noted by the Committee, this combination is one of several proposed in the WHO treatment guidelines, is a preferred combination for first-line treatment, and can be used in most subpopulations of HIV patients, including pregnant women and in children. Several products of adequate quality exist, containing appropriate doses of the components and there have been clinical studies using the components of the FDC at the same doses as well as several observational studies using this FDC. There is substantial experience of use of this product in resource-poor settings, but there is significant toxicity associated with this combination that may eventually lead to a decline in its use. It is widely available. The Committee also noted the advice from the HIV/AIDS Department that the FDC containing 40 mg stavudine would no longer be recommended, due to excess toxicity of the higher dose.

The Committee therefore recommended that the FDC containing stavudine 30 mg, lamivudine and nevirapine should be added to the Model List, but not the product containing stavudine 40 mg.

4.5.4.4 Addition of emtricitabine and tenofovir disoproxil fumarate fixed-dose combination

In 2005, the Expert Committee considered an application from the manufacturer for tenofovir (TDF) and emtricitabine as an FDC. At that meeting, the Committee noted “the fixed-dose combination had only recently been

approved by the US Food and Drug Administration, but that it is increasingly being used in national programmes. However, it would be illogical to consider the combination so long as the individual medicines had not been added to the Model List. The Committee concluded that listing of the combination at this stage would be premature, and decided to defer its decision because of the lack of information, for example, in comparison with lamivudine.”

Tenofovir and emtricitabine are listed in current WHO treatment guidelines for adults (18) as one option for first-line combination treatment as part of the NRTI backbone, and as an alternative to abacavir (ABC).

Expert reviews of the application were prepared by: Mr Andy Gray and Dr Lenita Wannmacher.¹

The evidence for comparative effectiveness and safety in this application consists of trials that were the basis of the USA’s regulatory approval of the FDC and two studies of bioequivalence and pharmacokinetics. It is not clear that any of the large trials used the proposed FDC. Safety data based on the use of the components individually and in combination, not as an FDC, is as presented in the applications for the single components. There is no evidence of use of this combination in resource-poor settings. The Committee noted that differential pricing of the FDC is proposed through an access programme: 30 days supply for US\$ 26.25. No formal cost-effectiveness evaluation was provided.

The Committee noted that this combination is one of several proposed in the WHO treatment guidelines, and is one combination for first-line treatment. The combination can be used in adult HIV patients but not children; there is limited information about its use in pregnant women. It is specifically recommended for use in patients co-infected with hepatitis B virus (HBV). One product of adequate quality exists, containing appropriate doses of the components, and there have been clinical studies using the components of the FDC at the same doses, but no clinical studies of the use of the FDC; there are also bioequivalence and pharmacokinetic studies. There is limited experience of use of this product in resource-poor settings.

The Committee therefore decided to add the combination of tenofovir and emtricitabine to the core list, noting particularly its utility in patients with HBV co-infection and with an accompanying note that 3TC is an acceptable alternative to FTC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of ARVs.

¹ Dr Lenita Wannmacher, Department of Clinical Pharmacology, School of Medicine, University of Passo Fundo, Teixeira Soares, Rio Grande do Sul, Brazil, is a Member of the Expert Committee.

4.5.4.5 **Addition of efavirenz, emtricitabine and tenofovir disoproxil fumarate FDC tablet**

A new application for a new FDC medicine, tablets containing 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir, to be listed in section 6.4.2 Antiretrovirals, as a combination of NRTIs and NNRTIs has been submitted by Merck Sharp & Dohme, France. The Committee received the letter from Merck as a late paper.

Efavirenz, tenofovir and emtricitabine are listed in current WHO treatment guidelines for adults (18) as one option for first-line combination treatment. As stated in the application, the triple combination has so far been registered in the USA only, although other regulatory approvals are being sought.

Expert reviews of the application were prepared by: Dr Lenita Wannmacher. Additional supporting statements were received from the Access to Essential Medicines Campaign, Médecins Sans Frontières.

The evidence for comparative effectiveness and safety in this application consisted of two studies: Study 934, published by Gallant et al. 2006 (36) and an observational study, ANRS 1207 in 40 subjects (presented as a poster only). Neither study used the proposed FDC. Gallant et al. compared treatment with the three components given separately with a FDC of AZT/3TC plus efavirenz, and the observational study appears to have used the individual components. Evidence of safety was based on the use of the components individually and in combination, not as an FDC, and is as presented in the other applications. Postmarketing safety reports from the use of the FDC were also provided but they reported adverse events only and were unquantified. Causality in relation to use of the FDC was not assessed. There was no evidence of use of this combination in resource-poor settings. The Committee noted that differential pricing of the FDC is proposed through an access programme, although the details were not provided in the application.

The Committee noted that this combination is one of several proposed in the WHO treatment guidelines, and is one combination for first-line treatment. The combination can be used in adult HIV patients but not children; efavirenz should not be used in pregnant women. It is specifically recommended for use in patients co-infected with HBV. One product of adequate quality exists, containing appropriate doses of the components and there has been one clinical study using the components of the FDC at the same doses and a small observational study using this FDC.

The Committee therefore decided this FDC should be added to the core list, noting particularly its utility in patients with HBV co-infection.

4.6 **New section under 6.4.3: Addition of new section and medicine ribavirin**

An application has been received from the Department of Epidemic and Pandemic Alert and Response (CDS/EPR) at WHO for the inclusion of ribavirin on the Model List for the treatment of viral haemorrhagic fevers (VHF) particularly Lassa fever (LF), Argentine haemorrhagic fever (AHF), Crimean-Congo haemorrhagic fever (CCHF) and haemorrhagic fever with renal syndrome (HFRS). The listing is as an individual medicine.

Expert reviews of the application were prepared by: Dr Lisa Bero.¹ Additional statements were received from Médecins Sans Frontières.

The Committee noted that the application provides a comprehensive review of the available clinical data on the use of ribavirin for the nominated haemorrhagic fevers. Most of the evidence is derived from case series and there have been few randomized or placebo controlled studies to assess the efficacy of ribavirin. The data generally suggest that ribavirin shortens the course of illness and reduces mortality rates from LF, CCHF and HFRS. While it has been suggested that further studies are required to establish the effectiveness of ribavirin, haemorrhagic fevers are associated with high morbidity and mortality, and there are few treatment options. The application notes a wide range of prices for ribavirin.

Given the potential benefits of treatment and the manageable side-effect profile of ribavirin, the Committee agreed to list ribavirin tablets and injection on the Model List. The Committee noted that even at the nominated prices, access in some country settings would remain a problem.

4.7 **Late item: antiviral medicines for pandemic influenza**

Dr Noël Cranswick² and Dr Thamizhanban Pillay³ excused themselves during discussion of this item.

The Committee noted the memo from the WHO Global Influenza Programme: GIP, “Possibility of inclusion of influenza-specific antivirals to the Model List” and acknowledged the problem stated in the paper. The Committee noted that this situation highlights the need for a process for making decisions between meetings and would welcome applications for antivirals for pandemic situations.

¹ Dr Lisa Bero, University of California, San Francisco, USA, is a Member of the Expert Committee.

² Dr Noël Cranswick, Clinical Pharmacology Department, Royal Children's Hospital, Parkville, Victoria, Australia, is a Member of the Expert Committee.

³ Dr Thamizhanban Pillay, Pharmaceutical Economic Evaluation, National Department of Health, Pretoria, South Africa, participated as Temporary Adviser to the Expert Committee.

4.8 Section 6.5.2: Antileishmaniasis: addition of paromomycin

Medicines for treating leishmaniasis have been on the Model List since its first edition and the currently listed medicines are meglumine antimoniate (core list) and pentamidine and amphotericin B (complementary list). The Institute for OneWorld Health, San Francisco, USA, has submitted a new application for a new medicine to be listed for leishmaniasis, paromomycin. The dosage form and strength proposed is a solution for intramuscular injection containing 375 mg/ml paromomycin base as a 2-ml ampoule (750 mg of paromomycin base present as the sulfate). Paromomycin is an aminoglycoside antibiotic identical to aminosidine (37) which was first shown to have antileishmanial activity in the early 1960s.

The application provided a summary of the evidence based primarily on the phase III clinical trial (38), but as noted by the Committee, did not cover all published literature. In the Phase III trial, paromomycin (11 mg/kg paromomycin base for 21 days) was shown to be comparable with amphotericin B (1 mg/kg intravenously every other day for 30 days). The final cure rate in patients treated with paromomycin was equivalent to that of patients treated with amphotericin B. In another study, paromomycin was shown to be more effective than sodium stibogluconate (final cure rates of 93%–97% versus 63%) (39). Combinations of paromomycin with antimony compounds were found to be highly efficacious (40–42).

The application provided a review of safety information. Overall, ototoxicity, nephrotoxicity and elevations of liver enzymes are noted, but do not appear to be clinically relevant and may be reversible. Nephrotoxicity was shown to be less of a problem with paromomycin than with amphotericin B. Currently, a post-approval Phase IV trial is being conducted in India.

In summary, paromomycin has been found to be effective in terms of effect on standard end-points, such as initial and final cure, for the treatment of visceral leishmaniasis in children and adults. The Committee considered the additional evidence supporting safety and efficacy that was not included in the application, as noted above. The safety profile is well-characterized in randomized trials and during the period of approximately 40 years of its use for treating various bacterial and protozoal infections, including leishmaniasis. Once daily intramuscular administration for 21 days offers greater suitability than sodium stibogluconate (30 days) and amphotericin B (intravenous, 30 days). Paromomycin appears to be the most cost-effective treatment among all available alternatives. Leishmaniasis is a neglected disease. The Committee therefore recommended adding paromomycin to the core Model List.

4.9 Section 6.5.3: Antimalarial medicines

4.9.1 Review of section 6.5.3: Antimalarial medicines

Expert reviews of the application were prepared by: Dr Eva M.A. Ombaka and Mr Andy Gray.

The WHO Malaria treatment guidelines (43) were published in early 2006. The main change to the treatment recommended in those guidelines was the recommendation that first-line treatment for malaria should be with combinations of medicines rather than monotherapy. Artemisinin combinations were recommended as first-line treatment although other combinations were also noted to be more effective than monotherapy.

The Global Malaria Programme, WHO, has therefore proposed several changes to the current Model List of medicines for malaria, to align it with the treatment guidelines. The following combinations are proposed as additions to the core list, for treatment of uncomplicated malaria:

- artesunate plus amodiaquine, co-packaged 50 mg + 153 mg
- artesunate plus mefloquine, co-packaged 50 mg + 250 mg
- artesunate plus sulfadoxine–pyramethamine, co-packaged 50 mg + 250 mg.

The addition of two new artesunate formulations for emergency use in severe malaria: intravenous artesunate (ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution) and rectal artesunate (capsules containing 100 mg or 400 mg sodium artesunate) was also considered, see Section 4.8.2.

The malaria treatment guidelines were based on a number of comprehensive systematic reviews of clinical evidence in relation to treatment of malaria, and these reviews formed the basis of this application.

The Committee noted that the evidence in the application had not been updated to include studies published in the last 18 months and that this recent evidence was comprehensively summarized in one of the expert reviews. In summary, the clinical evidence showed that:

- Combination therapy for uncomplicated malaria is superior to monotherapy (odds ratio (OR) 0.30, 95% CI, 0.26–0.36).
- Artemisinin-containing combination therapy (ACTs) may be superior to other combinations such as amodiaquine plus sulfadoxine–pyramethamine (OR 0.49, 95% CI, 0.27–0.87).
- Currently, there do not appear to be any differences in effectiveness between the different ACTs.
- 6-dose regimens are superior to 4-dose regimens (based on polymerase-chain-reaction-adjusted cure at 28 days).

The guidelines also include recommendations about treatment of pregnant women and children with ACTs, based on reviews of observational and pharmacokinetic studies. ACTs are recommended as effective and safe in the second and third trimester of pregnancy, and artemether–lumefantrine can be used in children with a body weight > 5 kg rather than > 10 kg.

The main safety issues relate to the adverse effects of amodiaquine and mefloquine; the adverse effects of both products have been well characterized. It is also important to note that the concerns about adverse effects of these products arose when they were being used for prophylaxis. However, there are continuing reports of adverse reactions with both amodiaquine and mefloquine.

The regulatory status of the products proposed for addition was unclear. The Committee noted that the application was primarily for co-blistered packaged preparations and no true FDCs currently exist. The Committee also considered several other changes to the list of antimalarial medicines that would be required to ensure consistency of listing with the treatment guidelines, that were not considered in the proposal from the Global Malaria Programme.

Having considered the proposal, and in the light of the policy of listing FDC products, the Committee decided to comprehensively amend the list of medicines for malaria as follows:

- To include amodiaquine, artemether + lumefantrine, mefloquine, doxycycline, primaquine, quinine and sulfadoxine + pyrimethamine oral dosage forms on the core list, with notes for each describing the appropriate combinations.
- To amend the note regarding the use of artemether + lumefantrine in pregnant women (to restrict use only in the first trimester of pregnancy) and in children (to note that use is possible in children of > 5 kg).
- To maintain chloroquine on the core list, but for use only in the treatment of *P. vivax*, *P. ovale* and *P. malariae* infections.
- To delete chloroquine injection, on the basis that it is no longer recommended for use in severe malaria.
- To amend the list of treatments for prophylaxis to limit the use of chloroquine to central American regions and for prophylaxis of *P. vivax*, *P. ovale* and *P. malariae* infections.

The Committee noted that rapid development of high-quality FDCs to meet the treatment needs for malaria would be highly desirable, and it would welcome applications for such products, once they exist. In addition, the Committee recommended rigorous trials of these FDCs as well as noting the potential advice available for drug development and regulatory approvals through existing regulatory procedures such as Article 58 of Regulation (EC) No 726/2004 1.

8. Antineoplastic, immunosuppressives and medicines used in palliative care (*continued*)

<i>calcium folinate</i>	Injection: 3 mg/ml in 10-ml ampoule. Tablet: 15 mg.
<i>chlorambucil</i>	Tablet: 2 mg.
<i>cisplatin</i>	Powder for injection: 10 mg; 50 mg in vial.
<i>cyclophosphamide</i>	Powder for injection: 500 mg in vial. Tablet: 25 mg.
<i>cytarabine</i>	Powder for injection: 100 mg in vial.
<i>dacarbazine</i>	Powder for injection: 100 mg in vial.
<i>dactinomycin</i>	Powder for injection: 500 micrograms in vial.
<i>daunorubicin</i>	Powder for injection: 50 mg (as hydrochloride) in vial.
<i>doxorubicin</i>	Powder for injection: 10 mg; 50 mg (hydrochloride) in vial.
<i>etoposide</i>	Capsule: 100 mg. Injection: 20 mg/ml in 5-ml ampoule.
<i>fluorouracil</i>	Injection: 50 mg/ml in 5-ml ampoule.
<i>mercaptopurine</i>	Tablet: 50 mg.
<i>methotrexate</i>	Powder for injection: 50 mg (as sodium salt) in vial. Tablet: 2.5 mg (as sodium salt).
<i>procarbazine</i>	Capsule: 50 mg (as hydrochloride).
<i>vinblastine</i>	Powder for injection: 10 mg (sulfate) in vial.
<i>vincristine</i>	Powder for injection: 1 mg; 5 mg (sulfate) in vial.

8.3 Hormones and antihormones*Complementary List*

<i>dexamethasone</i>	Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.
<i>hydrocortisone</i>	Powder for injection: 100 mg (as sodium succinate) in vial.
<input type="checkbox"/> <i>prednisolone*</i>	Tablet: 5 mg; 25 mg. * There is no evidence for complete clinical similarity between prednisolone and dexamethasone at high doses.
<i>tamoxifen</i>	Tablet: 10 mg; 20 mg (as citrate).

8. Antineoplastic, immunosuppressives and medicines used in palliative care *(continued)*

8.4 Medicines used in palliative care

The WHO Expert Committee recognizes the importance of listing specific medicines in the Palliative Care Section. Some medicines currently used in palliative care are included in the relevant sections of the Model List, according to their therapeutic use, e.g. analgesics. The Guidelines for Palliative Care that were referenced in the previous list are in need of update. The Committee expects applications for medicines needed for palliative care to be submitted for the next meeting.

9. Antiparkinsonism medicines

biperiden	Injection: 5 mg (lactate) in 1-ml ampoule. Tablet: 2 mg (hydrochloride).
levodopa + □ carbidopa	Tablet: 100 mg + 10 mg; 250 mg + 25 mg.

10. Medicines affecting the blood

10.1 Antianaemia medicines

ferrous salt	Oral liquid: equivalent to 25 mg iron (as sulfate)/ml. Tablet: equivalent to 60 mg iron.
ferrous salt + folic acid	Tablet equivalent to 60 mg iron + 400 micrograms folic acid (nutritional supplement for use during pregnancy).
folic acid	Tablet: 1 mg; 5 mg.
hydroxocobalamin	Injection: 1 mg in 1-ml ampoule.

10.2 Medicines affecting coagulation

heparin sodium	Injection: 1000 IU/ml; 5000 IU/ml; 20,000 IU/ml in 1-ml ampoule.
phytomenadione	Injection: 10 mg/ml in 5-ml ampoule. Tablet: 10 mg.
protamine sulfate	Injection: 10 mg/ml in 5-ml ampoule.
□ warfarin	Tablet: 1 mg; 2 mg; 5 mg (sodium salt).

11. Blood products and plasma substitutes

11.1 Plasma substitutes

□ dextran 70*	Injectable solution: 6%. * Polygeline, injectable solution, 3.5% is considered as equivalent.
---------------	--

11.2 Plasma fractions for specific use

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). (WHO Technical Report Series, No. 840, 1994, Annex 2).

11. Blood products and plasma substitutes (continued)

Complementary List

<i>human normal immunoglobulin</i>	Intramuscular administration: 16% protein solution. Intravenous administration: 5%, 10% protein solution.
□ <i>factor VIII concentrate</i>	Dried.
□ <i>factor IX complex (coagulation factors, II, VII, IX, X) concentrate</i>	Dried.

12. Cardiovascular medicines

12.1 Antianginal medicines

□ atenolol	Tablet: 50 mg; 100 mg.
glyceryl trinitrate	Tablet (sublingual): 500 micrograms.
□ isosorbide dinitrate	Tablet (sublingual): 5 mg.
verapamil	Tablet: 40 mg; 80 mg (hydrochloride).

12.2 Antiarrhythmic medicines

This subsection will be reviewed at the next meeting of the Expert Committee.

□ atenolol	Tablet: 50 mg; 100 mg.
digoxin	Injection: 250 micrograms/ml in 2-ml ampoule. Oral liquid: 50 micrograms/ml. Tablet: 62.5 micrograms; 250 micrograms.
epinephrine (adrenaline)	Injection: 100 micrograms/ml (as acid tartrate or hydrochloride) in 10-ml ampoule.
lidocaine	Injection: 20 mg (hydrochloride)/ml in 5-ml ampoule.
verapamil	Injection: 2.5 mg (hydrochloride)/ml in 2-ml ampoule. Tablet: 40 mg; 80 mg (hydrochloride).

Complementary List

□ <i>procainamide</i>	Injection: 100 mg (hydrochloride)/ml in 10-ml ampoule.
□ <i>quinidine</i>	Tablet: 200 mg (sulfate).

12.3 Antihypertensive medicines

□ amlodipine	Tablet: 5 mg.
□ atenolol	Tablet: 50 mg; 100 mg.
□ enalapril	Tablet: 2.5 mg.

12. Cardiovascular medicines (continued)

hydralazine*	Powder for injection: 20 mg (hydrochloride) in ampoule. Tablet: 25 mg, 50 mg (hydrochloride). * Hydralazine is listed for use in the acute management of severe 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.
<input type="checkbox"/> hydrochlorothiazide	Tablet (scored): 25 mg.
methyldopa*	Tablet: 250 mg. * 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.

Complementary List

sodium nitroprusside	Powder for infusion: 50 mg in ampoule.
----------------------	--

12.4 Medicines used in heart failure

This subsection will be reviewed at the next meeting of the Expert Committee.

digoxin	Injection: 250 micrograms/ml in 2-ml ampoule. Oral liquid: 50 micrograms/ml. Tablet: 62.5 micrograms; 250 micrograms.
<input type="checkbox"/> enalapril	Tablet: 2.5 mg.
<input type="checkbox"/> furosemide	Injection: 10 mg/ml in 2-ml ampoule. Tablet: 40 mg.
<input type="checkbox"/> hydrochlorothiazide	Tablet (scored): 25 mg.

Complementary List

dopamine	Injection: 40 mg/ml (hydrochloride) in 5-ml vial.
----------	---

12.5 Antithrombotic medicines

acetylsalicylic acid	Tablet: 100 mg.
<i>Complementary List</i>	
streptokinase	Powder for injection: 1.5 million IU in vial.

12.6 Lipid-lowering agents

<input type="checkbox"/> simvastatin*	Tablet: 5 mg; 10 mg; 20 mg; 40 mg. * For use in high-risk patients.
---------------------------------------	--

13. Dermatological medicines (topical)

13.1 Antifungal medicines

benzoic acid + salicylic acid	Ointment or cream: 6% + 3%.
□ miconazole	Ointment or cream: 2% (nitrate).
sodium thiosulfate	Solution: 15%.

Complementary List

<i>selenium sulfide</i>	Detergent-based suspension: 2%.
-------------------------	---------------------------------

13.2 Anti-infective medicines

□ methylrosanilinium chloride (gentian violet)	Aqueous solution: 0.5%. Tincture: 0.5%.
neomycin sulfate + □ bacitracin	Ointment: 5 mg neomycin sulfate + 250 IU bacitracin zinc/g.
potassium permanganate	Aqueous solution: 1:10 000.
silver sulfadiazine	Cream: 1%, in 500-g container.

13.3 Anti-inflammatory and antipruritic medicines

□ betamethasone	Ointment or cream: 0.1% (as valerate).
□ calamine lotion	Lotion.
□ hydrocortisone	Ointment or cream: 1% (acetate).

13.4 Astringent medicines

aluminium diacetate	Solution: 5%.
---------------------	---------------

13.5 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	Lotion or cream: 5%.
coal tar	Solution: 5%.
dithranol	Ointment: 0.1%-2%.
fluorouracil	Ointment: 5%.
□ podophyllum resin	Solution: 10-25%.
salicylic acid	Solution: 5%.
urea	Ointment or cream: 10%.

13.6 Scabicides and pediculicides

□ benzyl benzoate	Lotion: 25%.
permethrin	Cream: 5%. Lotion: 1%.

14. Diagnostic agents

14.1 Ophthalmic medicines

fluorescein Eye drops: 1% (sodium salt).

tropicamide Eye drops: 0.5%.

14.2 Radiocontrast media

amidotrizoate Injection: 140-420 mg iodine (as sodium or meglumine salt)/ml in 20-ml ampoule.

barium sulfate Aqueous suspension.

iohexol Injection: 140-350 mg iodine/ml in 5-ml; 10-ml; 20-ml ampoules.

Complementary List

meglumine iotroxate Solution: 5-8 g iodine in 100-250 ml.

15. Disinfectants and antiseptics

15.1 Antiseptics

chlorhexidine Solution: 5% (digluconate) for dilution.

ethanol Solution: 70% (denatured).

polyvidone iodine Solution: 10%.

15.2 Disinfectants

chlorine base compound Powder: (0.1% available chlorine) for solution.

chloroxylenol Solution: 4.8%.

glutaral Solution: 2%.

16. Diuretics

amiloride Tablet: 5 mg (hydrochloride).

furosemide Injection: 10 mg/ml in 2-ml ampoule.
Tablet: 40 mg.

hydrochlorothiazide Tablet (scored): 25 mg.

mannitol Injectable solution: 10%; 20%.

spironolactone Tablet: 25 mg.

17. Gastrointestinal medicines

17.1 Antacids and other antiulcer medicines

aluminium hydroxide Oral liquid: 320 mg/5 ml.
Tablet: 500 mg.

17. Gastrointestinal medicines (continued)

- ranitidine
Injection: 25 mg/ml in 2-ml ampoule.
Oral liquid: 75 mg/5 ml.
Tablet: 150 mg (as hydrochloride).
- magnesium hydroxide
Oral liquid: equivalent to 550 mg magnesium oxide/10 ml.

17.2 Antiemetic medicines

- metoclopramide
Injection: 5 mg (hydrochloride)/ml in 2-ml ampoule.
Tablet: 10 mg (hydrochloride).
- promethazine
Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule.
Oral liquid: 5 mg (hydrochloride)/5 ml.
Tablet: 10 mg; 25 mg (hydrochloride).

17.3 Anti-inflammatory medicines

- sulfasalazine
Retention enema.
Suppository: 500 mg.
Tablet: 500 mg.

Complementary List

- hydrocortisone
Retention enema.
Suppository: 25 mg (acetate). (the only applies to hydrocortisone retention enema).

17.4 Laxatives

- senna
Tablet: 7.5 mg (sennosides)
(or traditional dosage forms).

17.5 Medicines used in diarrhoea

17.5.1 Oral rehydration

- oral rehydration salts*
- | | |
|-------------------------------|------------------|
| glucose: | 75 mEq |
| sodium: | 75 mEq or mmol/l |
| chloride: | 65 mEq or mmol/l |
| potassium: | 20 mEq or mmol/l |
| citrate: | 10 mmol/l |
| osmolarity: | 245 mOsm/l |
| glucose: | 13.5 g/l |
| sodium chloride: | 2.6 g/l |
| potassium chloride: | 1.5 g/l |
| trisodium citrate dihydrate*: | 2.9 g/l |

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

* In cases of cholera a higher concentration of sodium may be required.

17. Gastrointestinal medicines (continued)

17.5.2 Medicines for diarrhoea in children

zinc sulfate*

Oral liquid: in 10 mg per unit dosage forms.
Tablet: in 10 mg per unit dosage forms.

* In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts.

17.5.3 Antidiarrhoeal (symptomatic) medicines in adults

codeine*

Tablet: 30 mg (phosphate).

* The role of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee.

18. Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes

Addison's disease is a rare condition; adrenal hormones are already included in section 3.

18.2 Androgens

Complementary List

testosterone

Injection: 200 mg (enantate) in 1-ml ampoule.

18.3 Contraceptives

18.3.1 Oral hormonal contraceptives

□ ethinylestradiol + □ levonorgestrel

Tablet: 30 micrograms + 150 micrograms.

□ ethinylestradiol + □ norethisterone

Tablet: 35 micrograms + 1.0 mg.

levonorgestrel

Tablet: 30 micrograms; 750 micrograms (pack of two); 1.5 mg.

18.3.2 Injectable hormonal contraceptives

medroxyprogesterone acetate

Depot injection: 150 mg/ml in 1-ml vial.

medroxyprogesterone acetate + estradiol cypionate

Injection: 25 mg + 5 mg.

norethisterone enantate

Oily solution: 200 mg/ml in 1-ml ampoule.

18.3.3 Intrauterine devices

copper-containing device

18.3.4 Barrier methods

condoms

diaphragms

18.3.5 Implantable contraceptives

levonorgestrel-releasing implant

Two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg total).

18. Hormones, other endocrine medicines and contraceptives (continued)

18.4 Estrogens

□ ethinylestradiol*

Tablet: 10 micrograms; 50 micrograms.

* The public health relevance and/or comparative 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.

18.5 Insulins and other antidiabetic agents

glibenclamide

Tablet: 2.5 mg; 5 mg.

insulin injection (soluble)

Injection: 40 IU/ml in 10-ml vial; 100 IU/ml in 10-ml vial.

intermediate-acting insulin

Injection: 40 IU/ml in 10-ml vial;
100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin).

metformin

Tablet: 500 mg (hydrochloride).

18.6 Ovulation inducers

Complementary List

clomifene

Tablet: 50 mg (citrate).

18.7 Progestogens

norethisterone*

Tablet: 5 mg.

* The public health relevance and/or comparative 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.

Complementary List

*medroxyprogesterone acetate**

Tablet: 5 mg.

* The public health relevance and/or comparative 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.

18.8 Thyroid hormones and antithyroid medicines

levothyroxine

Tablet: 50 micrograms;
100 micrograms (sodium salt).

potassium iodide

Tablet: 60 mg.

□ propylthiouracil

Tablet: 50 mg.

19. Immunologicals

19.1 Diagnostic agents

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

tuberculin, purified protein derivative (PPD) Injection.

19.2 Sera and immunoglobulins

All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization. Forty-third report. (WHO Technical Report Series, No. 840, 1994, Annex 2).

anti-D immunoglobulin (human) Injection: 250 micrograms in single-dose vial.

antitetanus immunoglobulin (human) Injection: 500 IU in vial.

antivenom immunoglobulin* Injection.
* Exact type to be defined locally.

diphtheria antitoxin Injection: 10 000 IU; 20 000 IU in vial.

□ rabies immunoglobulin Injection: 150 IU/ml in vial.

19.3 Vaccines

Selection of vaccines from the Model List will need to be determined by each country after consideration of international recommendations, epidemiology and national priorities. The list below details the vaccines for which there is either a recommendation from the Strategic Advisory Group of Experts on Immunization (SAGE) (http://www.who.int/immunization/sage_conclusions/en/index.html) and/or a WHO position paper (<http://www.who.int/immunization/documents/positionpapers/en/index.html>). This site will be updated as new position papers are published and contains the most recent information and recommendations.

All vaccines should comply with the WHO Requirements for Biological Substances.

BCG vaccine

cholera vaccine

diphtheria vaccine

hepatitis A vaccine

hepatitis B vaccine

Haemophilus influenzae type b vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

21. Ophthalmological preparations (continued)

21.4 Miotics and antiglaucoma medicines

- acetazolamide Tablet: 250 mg.
- pilocarpine Solution (eye drops): 2%; 4% (hydrochloride or nitrate).
- timolol Solution (eye drops): 0.25%; 0.5% (as maleate).

21.5 Mydriatics

- atropine Solution (eye drops): 0.1%; 0.5%, 1% (sulfate).

Complementary List

- epinephrine (adrenaline)* Solution (eye drops): 2% (as hydrochloride).
-

22. Oxytocics and antioxytocics

22.1 Oxytocics

- ergometrine Injection: 200 micrograms (hydrogen maleate) in 1-ml ampoule.

- oxytocin Injection: 10 IU in 1-ml ampoule.

Complementary List

- misoprostol* Vaginal tablet: 25 micrograms.

- mifepristone* – misoprostol** Tablet 200 mg – tablet 200 micrograms.

* Requires close medical supervision.

Where permitted under national law and where culturally acceptable.

22.2 Antioxytocics (tocolytics)

- nifedipine Immediate release capsule: 10 mg.
-

23. Peritoneal dialysis solution

Complementary List

- intraperitoneal dialysis solution (of appropriate composition)* Parenteral solution.
-

24. Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders

- chlorpromazine Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule.
Oral liquid: 25 mg (hydrochloride)/5 ml.
Tablet: 100 mg (hydrochloride).
- fluphenazine Injection: 25 mg (decanoate or enantate) in 1-ml ampoule.

25. Medicines acting on the respiratory tract (continued)

□ salbutamol	Inhalation (aerosol): 100 micrograms (as sulfate) per dose. Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule. Oral liquid: 2 mg/5 ml. Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml. Tablet: 2 mg; 4 mg (as sulfate).
--------------	---

25.2 Other medicines acting on the respiratory tract

caffeine citrate	Injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml). Oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml).
------------------	--

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

26.1 Oral

oral rehydration salts	See section 17.5.1.
potassium chloride	Powder for solution.

26.2 Parenteral

glucose	Injectable solution: 5%; 10% isotonic; 50% hypertonic.
glucose with sodium chloride	Injectable solution: 4% glucose, 0.18% sodium chloride (equivalent to Na ⁺ 30 mmol/l, Cl ⁻ 30 mmol/l).
potassium chloride	Solution: 11.2% in 20-ml ampoule (equivalent to K ⁺ 1.5 mmol/ml, Cl ⁻ 1.5 mmol/ml).
sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na ⁺ 154 mmol/l, Cl ⁻ 154 mmol/l).
sodium hydrogen carbonate	Injectable solution: 1.4% isotonic (equivalent to Na ⁺ 167 mmol/l, HCO ₃ ⁻ 167 mmol/l). Solution: 8.4% in 10-ml ampoule (equivalent to Na ⁺ 1000 mmol/l, HCO ₃ ⁻ 1000 mmol/l).
□ sodium lactate, compound solution	Injectable solution.

26.3 Miscellaneous

water for injection	2-ml; 5-ml; 10-ml ampoules.
---------------------	-----------------------------

27. Vitamins and minerals

ascorbic acid	Tablet: 50 mg.
□ ergocalciferol	Capsule or tablet: 1.25 mg (50 000 IU). Oral liquid: 250 micrograms/ml (10 000 IU/ml).

27. Vitamins and minerals *(continued)*

iodine	Capsule: 200 mg. Iodized oil: 1 ml (480 mg iodine); 0.5 ml (240 mg iodine) in ampoule (oral or injectable); 0.57 ml (308 mg iodine) in dispenser bottle.
□ nicotinamide	Tablet: 50 mg.
pyridoxine	Tablet: 25 mg (hydrochloride).
retinol	Capsule: 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser. Tablet (sugar-coated): 10 000 IU (as palmitate). Water-miscible injection: 100 000 IU (as palmitate) in 2-ml ampoule.
riboflavin	Tablet: 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	Tablet: 50 mg (hydrochloride).
<i>Complementary List</i>	
<i>calcium gluconate</i>	Injection: 100 mg/ml in 10-ml ampoule.

Annex 3

The Anatomical Therapeutic Chemical (ATC) classification system

The following list provides the corresponding Anatomical Therapeutic Chemical (ATC) classification codes for all items on the 15th WHO Model List of Essential Medicines, sorted by ATC code number.

ATC code	ATC group/medicine or item	Section
A	ALIMENTARY TRACT AND METABOLISM	
A02	Drugs for acid related disorders	
A02A	Antacids	
<i>A02AA</i>	<i>Magnesium compounds</i>	
A02AA04	magnesium hydroxide	17.1
<i>A02AB</i>	<i>Aluminium compounds</i>	
A02AB01	aluminium hydroxide	17.1
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	
<i>A02BA</i>	<i>H₂-receptor antagonists</i>	
A02BA02	ranitidine	17.1
<i>A02BB</i>	<i>Prostaglandins</i>	
A02BB01	misoprostol	22.1
A03	Drugs for functional gastrointestinal disorders	
A03B	Belladonna and derivatives, plain	
<i>A03BA</i>	<i>Belladonna alkaloids, tertiary amines</i>	
A03BA01	atropine	1.3; 4.2
A03F	Propulsives	
<i>A03FA</i>	<i>Propulsives</i>	
A03FA01	metoclopramide	17.2
A06	Laxatives	
A06A	Laxatives	
<i>A06AB</i>	<i>Contact laxatives</i>	
A06AB06	senna*	17.4
A07	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	
A07A	Intestinal antiinfectives	
<i>A07AA</i>	<i>Antibiotics</i>	
A07AA02	nystatin	6.3
A07AA06	paromomycin	6.5.2

ATC code	ATC group/medicine or item	Section
A07B	Intestinal adsorbents	
A07BA	<i>Charcoal preparations</i>	
A07BA01	charcoal, activated*	4.1
A07C	Electrolytes with carbohydrates	
A07CA	<i>oral rehydration salts*</i>	17.5.1; 26.1
A07E	Intestinal antiinflammatory agents	
A07EA	<i>Corticosteroids for local use</i>	
A07EA02	hydrocortisone	17.3
A07EC	<i>Aminosalicylic acid and similar agents</i>	
A07EC01	sulfasalazine	2.4; 17.3
A10	Drugs used in diabetes	
A10A	Insulins and analogues	
A10AB	<i>Insulins and analogues, fast-acting</i>	
A10AB	insulin injection (soluble)*	18.5
A10AC	<i>Insulins and analogues, intermediate-acting</i>	
A10AC	insulin, intermediate-acting*	18.5
A10B	Oral blood glucose lowering drugs	
A10BA	<i>Biguanides</i>	
A10BA02	metformin	18.5
A10BB	<i>Sulfonamides, urea derivatives</i>	
A10BB01	glibenclamide	18.5
A11	Vitamins	
A11C	Vitamin A and D, incl. combinations of the two	
A11CA	<i>Vitamin A, plain</i>	
A11CA01	retinol	27
A11CC	<i>Vitamin D and analogues</i>	
A11CC01	ergocalciferol	27
A11D	Vitamin B₁, plain and in combination with vitamin B₆ and B₁₂	
A11DA	<i>Vitamin B₁, plain</i>	
A11DA01	thiamine	27
A11G	Ascorbic acid (vitamin C), incl. combinations	
A11GA	<i>Ascorbic acid (vitamin C), plain</i>	
A11GA01	ascorbic acid	27
A11H	Other plain vitamin preparations	
A11HA	<i>Other plain vitamin preparations</i>	
A11HA01	nicotinamide	27
A11HA02	pyridoxine	27
A11HA04	riboflavin	27

ATC code	ATC group/medicine or item	Section
A12	Mineral supplements	
A12A	Calcium	
<i>A12AA</i>	<i>Calcium</i>	
A12AA03	calcium gluconate	4.2; 27
A12C	Other mineral supplements	
<i>A12CB</i>	<i>Zinc</i>	
A12CB01	zinc sulfate	17.5.2
<i>A12CD</i>	<i>Fluoride</i>	
A12CD01	sodium fluoride	27
<i>A12CX</i>	<i>Other mineral products</i>	
A12CX	iodine*	27
B	BLOOD AND BLOOD FORMING ORGANS	
B01	Antithrombotic agents	
B01A	Antithrombotic agents	
<i>B01AA</i>	<i>Vitamin K antagonists</i>	
B01AA03	warfarin	10.2
<i>B01AB</i>	<i>Heparin group</i>	
B01AB01	heparin sodium*	10.2
B01AC	Platelet aggregation inhibitors excl. heparin	
B01AC06	acetylsalicylic acid	12.5
<i>B01AD</i>	<i>Enzymes</i>	
B01AD01	streptokinase	12.5
B02	Antihemorrhagics	
B02B	Vitamin K and other hemostatics	
<i>B02BA</i>	<i>Vitamin K</i>	
B02BA01	phytomenadione	10.2
<i>B02BD</i>	<i>Blood coagulation factors</i>	
B02BD01	factor IX complex (coagulation factors II, VII, IX, X) concentrate*	11.2
B02BD02	factor VIII concentrate*	11.2
B03	Antianemic preparations	
B03A	ferrous salt*	10.1
B03A	Iron preparations	
<i>B03AD</i>	<i>Iron in combination with folic acid</i>	
B03AD	ferrous salt + folic acid*	10.1
B03B	Vitamin B₁₂ and folic acid	
B03BA	Vitamin B ₁₂ (cyanocobalamin and analogues)	
B03BA03	hydroxocobalamin	10.1
<i>B03BB</i>	<i>Folic acid and derivatives</i>	
B03BB01	folic acid	10.1

ATC code	ATC group/medicine or item	Section
B05	Blood substitutes and perfusion solutions	
B05A	Blood and related products	
<i>B05AA</i>	<i>Blood substitutes and plasma protein fractions</i>	
B05AA05	dextran 70*	11.1
B05AA06	polygeline*	11.1
B05B	I.V. solutions	
<i>B05BB</i>	<i>Solutions affecting the electrolyte balance</i>	
B05BB01	sodium lactate, compound solution*	26.2
B05BB02	glucose with sodium chloride*	26.2
<i>B05BC</i>	<i>Solutions producing osmotic diuresis</i>	
B05BC01	mannitol	16
B05D	Peritoneal dialytics	
<i>B05DA</i>	<i>intraperitoneal dialysis solution*</i>	23
B05X	I.V. solution additives	
<i>B05XA</i>	<i>Electrolyte solutions</i>	
B05XA01	potassium chloride	26.1; 26.2
B05XA02	sodium hydrogen carbonate*	26.2
B05XA03	sodium chloride	26.2
B05XA05	magnesium sulfate	5
C	CARDIOVASCULAR SYSTEM	
C01	Cardiac therapy	
C01A	Cardiac glycosides	
<i>C01AA</i>	<i>Digitalis glycosides</i>	
C01AA01	simvastatin	12.6
C01AA05	digoxin	12.2; 12.4
C01B	Antiarrhythmics, class I and III	
<i>C01BA</i>	<i>Antiarrhythmics, class Ia</i>	
C01BA01	quinidine	12.2
C01BA02	procainamide	12.2
<i>C01BB</i>	<i>Antiarrhythmics, class Ib</i>	
C01BB01	lidocaine	12.2
C01C	Cardiac stimulants excl. cardiac glycosides	
<i>C01CA</i>	<i>Adrenergic and dopaminergic agents</i>	
C01CA04	dopamine	12.4
C01CA24	epinephrine (adrenaline)	3; 12.2; 25.1
C01D	Vasodilators used in cardiac diseases	
<i>C01DA</i>	<i>Organic nitrates</i>	
C01DA02	glyceryl trinitrate	12.1
C01DA08	isosorbide dinitrate	12.1

ATC code	ATC group/medicine or item	Section
C02	Antihypertensives	
C02A	Antiadrenergic agents, centrally acting	
<i>C02AB</i>	<i>Methyldopa</i>	
C02AB01	methyldopa*	12.3
C02D	Arteriolar smooth muscle, agents acting on	
<i>C02DB</i>	<i>Hydrazinophthalazine derivatives</i>	
C02DB02	hydrazaline	12.3
C02DD	Nitroferricyanide derivatives	
C02DD01	sodium nitroprusside*	12.3
C03	Diuretics	
C03A	Low-ceiling diuretics, thiazides	
<i>C03AA</i>	<i>Thiazides, plain</i>	
C03AA03	hydrochlorothiazide	12.3;12.4;16
C03C	High-ceiling diuretics	
<i>C03CA</i>	<i>Sulfonamides, plain</i>	
C03CA01	furosemide	12.4; 16
C03D	Potassium-sparing agents	
<i>C03DA</i>	<i>Aldosterone antagonists</i>	
C03DA01	spironolactone	16
<i>C03DB</i>	<i>Other potassium-sparing agents</i>	
C03DB01	amiloride	16
C07	Beta blocking agents	
C07A	Beta blocking agents	
<i>C07AA</i>	<i>Beta blocking agents, non-selective</i>	
C07AA05	propranolol	7.2
<i>C07AB</i>	<i>Beta blocking agents, selective</i>	
C07AB03	atenolol	12.1;12.2;12.3
C08	Calcium channel blockers	
C08C	Selective calcium channel blockers with mainly vascular effects	
<i>C08CA</i>	<i>Dihydropyridine derivatives</i>	
C08CA01	amlodipine	12.3
C08CA05	nifedipine	22.2
C08D	Selective calcium channel blockers with direct cardiac effects	
<i>C08DA</i>	<i>Phenylalkylamine derivatives</i>	
C08DA01	verapamil	12.1;12.2
C09	Agents acting on the renin-angiotensin system	
C09A	ACE inhibitors, plain	
<i>C09AA</i>	<i>ACE inhibitors, plain</i>	
C09AA02	enalapril	12.3;12.4

ATC code	ATC group/medicine or item	Section
D	DERMATOLOGICALS	
D01	Antifungals for dermatological use	
D01A	Antifungals for topical use	
<i>D01AA</i>	<i>Antibiotics</i>	
D01AA01	nystatin	6.3
<i>D01AC</i>	<i>Imidazole and triazole derivatives</i>	
D01AC02	miconazole	13.1
<i>D01AE</i>	<i>Other antifungals for topical use</i>	
D01AE02	methylrosanilinium chloride (gentian violet)*	13.2
D01AE12	salicylic acid	13.5
D01AE13	selenium sulfide	13.1
D01AE20	benzoic acid + salicylic acid*	13.1
D01B	Antifungals for systemic use	
<i>D01BA</i>	<i>Antifungals for systemic use</i>	
D01BA01	griseofulvin	6.3
D02	Emollients and protectives	
<i>D02A</i>	<i>Emollients and protectives</i>	
<i>D02AB</i>	<i>Zinc products</i>	
D02AB	calamine lotion*	13.3
<i>D02AE</i>	<i>Carbamide products</i>	
D02AE01	urea*	13.5
D05	Antipsoriatics	
D05A	Antipsoriatics for topical use	
<i>D05AA</i>	<i>Tars</i>	
<i>D05AA</i>	<i>coal tar*</i>	13.5
D05AC	Antracene derivatives	
D05AC01	dithranol	13.5
D06	Antibiotics and chemotherapeutics for dermatological use	
D06A	Antibiotics for topical use	
<i>D06AX</i>	<i>Other antibiotics for topical use</i>	
D06AX04	neomycin + bacitracin*	13.2
D06B	Chemotherapeutics for topical use	
<i>D06BA</i>	<i>Sulfonamides</i>	
D06BA01	silver sulfadiazine	13.2
<i>D06BB</i>	<i>Antivirals</i>	
D06BB04	podophyllum resin*	13.5
D07	Corticosteroids, dermatological preparations	
D07A	Corticosteroids, plain	
D07AA	Corticosteroids, weak (group I)	
D07AA02	hydrocortisone	13.3

ATC code	ATC group/medicine or item	Section
D07AC	Corticosteroids, potent (group III)	
D07AC01	betamethasone	13.3
D08	Antiseptics and disinfectants	
D08A	Antiseptics and disinfectants	
<i>D08AC</i>	<i>Biguanides and amidines</i>	
D08AC02	chlorhexidine	15.1
<i>D08AE</i>	<i>Phenol and derivatives</i>	
D08AE05	chloroxylenol	15.2
<i>D08AG</i>	<i>Iodine products</i>	
D08AG02	polyvidone iodine	15.1
<i>D08AX</i>	<i>Other antiseptics and disinfectants</i>	
D08AX	chlorine base compound*	15.2
D08AX06	potassium permanganate	13.2
D08AX08	ethanol	15.1
D10	Anti-acne preparations	
D10A	Anti-acne preparations for topical use	
<i>D10AE</i>	<i>Peroxides</i>	
D10AE01	benzoyl peroxide	13.5
<i>D10AX</i>	<i>Other anti-acne preparations for topical use</i>	
D10AX05	aluminium diacetate	13.4
G	GENITO URINARY SYSTEM AND SEX HORMONES	
G01	Gynecological antiinfectives and antiseptics	
G01A	Antiinfectives and antiseptics, excl. combinations with corticosteroids	
<i>G01AA</i>	<i>Antibiotics</i>	
G01AA01	nystatin	6.3
<i>G01AF</i>	<i>Imidazole derivatives</i>	
G01AF02	clotrimazole	6.3
G02	Other gynecologicals	
G02A	Oxytocics	
<i>G02AB</i>	<i>Ergot alkaloids</i>	
G02AB03	ergometrine	22.1
G02B	Contraceptives for topical use	
<i>G02BA</i>	<i>Intrauterine contraceptives</i>	
G02BA02	copper-containing device*	18.3.3
<i>G02BB</i>	<i>Intravaginal contraceptives</i>	
G02BB	diaphragms*	18.3.4

ATC code	ATC group/medicine or item	Section
G03	Sex hormones and modulators of the genital system	
G03A	Hormonal contraceptives for systemic use	
<i>G03AA</i>	<i>Progestogens and estrogens, fixed combinations</i>	
G03AA05	ethinylestradiol + norethisterone*	18.3.1
G03AA08	medroxyprogesterone and estrogen	18.3.1
<i>G03AB</i>	<i>Progestogens and estrogens, sequential preparations</i>	
G03AB03	ethinylestradiol + levonorgestrel*	18.3.1
<i>G03AC</i>	<i>Progestogens</i>	
G03AC01	norethisterone enantate*	18.3.2
G03AC03	levonorgestrel	18.3.1
	levonorgestrel-releasing implant	18.3.5
G03AC06	medroxyprogesterone acetate*	18.3.2; 18.7
G03B	Androgens	
<i>G03BA</i>	<i>3-oxoandrostens (4) derivatives</i>	
G03BA03	testosterone	18.2
G03C	Estrogens	
<i>G03CA</i>	<i>Natural and semisynthetic estrogens, plain</i>	
G03CA01	ethinylestradiol	18.4
G03D	Progestogens	
<i>G03DC</i>	<i>Estren derivatives</i>	
G03DC02	norethisterone	18.7
G03G	Gonadotropins and other ovulation stimulants	
<i>G03GB</i>	<i>Ovulation stimulants, synthetic</i>	
G03GB02	clomifene	18.6
G03X	Other sex hormones and modulators of the genital system	
<i>G03XB</i>	<i>Antiprogesterons</i>	
G03XB01	mifepristone	22.1
H	SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	
H01	Pituitary, hypothalamic hormones and analogues	
H01B	Posterior pituitary lobe hormones	
<i>H01BB</i>	<i>Oxytocin and analogues</i>	
H01BB02	oxytocin	22.1
H02	Corticosteroids for systemic use	
H02A	Corticosteroids for systemic use, plain	
<i>H02AB</i>	<i>Glucocorticoids</i>	
H02AB02	dexamethasone	3; 8.3
H02AB06	prednisolone	3; 8.3
H02AB09	hydrocortisone	3; 8.3

ATC code	ATC group/medicine or item	Section
H03	Thyroid therapy	
H03A	Thyroid preparations	
<i>H03AA</i>	<i>Thyroid hormones</i>	
H03AA01	levothyroxine*	18.8
H03B	Antithyroid preparations	
<i>H03BA</i>	<i>Thiouracils</i>	
H03BA02	propylthiouracil	18.8
H03C	Iodine therapy	
<i>H03CA</i>	<i>Iodine therapy</i>	
H03CA	potassium iodide*	6.3; 18.8
J	ANTIINFECTIVES FOR SYSTEMIC USE	
J01	Antibacterials for systemic use	
J01A	Tetracyclines	
<i>J01AA</i>	<i>Tetracyclines</i>	
J01AA02	doxycycline	6.2.2; 6.5.3.1; 6.5.3.2
J01B	Amphenicols	
<i>J01BA</i>	<i>Amphenicols</i>	
J01BA01	chloramphenicol	6.2.2
J01C	Beta-lactam antibacterials, penicillins	
<i>J01CA</i>	<i>Penicillins with extended spectrum</i>	
J01CA01	ampicillin	6.2.1
J01CA04	amoxicillin	6.2.1
<i>J01CE</i>	<i>Beta-lactamase sensitive penicillins</i>	
J01CE01	benzylpenicillin	6.2.1
J01CE02	phenoxymethylpenicillin	6.2.1
J01CE08	benzathine benzylpenicillin	6.2.1
J01CE09	procaine benzylpenicillin*	6.2.1
<i>J01CF</i>	<i>Beta-lactamase resistant penicillins</i>	
J01CF02	cloxacillin	6.2.1
<i>J01CR</i>	<i>Combinations of penicillins, incl. beta-lactamase inhibitors</i>	
J01CR02	amoxicillin + clavulanic acid*	6.2.1
J01D	Other beta-lactam antibacterials	
<i>J01DB</i>	<i>First-generation cephalosporins</i>	
J01DB04	cefazolin	6.2.1
<i>J01DD</i>	<i>Third-generation cephalosporins</i>	
J01DD02	ceftazidime	6.2.1
J01DD04	ceftriaxone	6.2.1
J01DD08	cefixime	6.2.1
<i>J01DH</i>	<i>Carbapenems</i>	
J01DH51	imipenem + cilastatin*	6.2.1

ATC code	ATC group/medicine or item	Section
J01E	Sulfonamides and trimethoprim	
<i>J01EA</i>	<i>Trimethoprim and derivatives</i>	
J01EA01	trimethoprim	6.2.2
<i>J01EC</i>	<i>Intermediate-acting sulfonamides</i>	
J01EC02	sulfadiazine	6.2.2
<i>J01EE</i>	<i>Combinations of sulfonamides and trimethoprim, incl. derivatives</i>	
J01EE01	sulfamethoxazole + trimethoprim	6.2.2; 6.5.4
J01F	Macrolides, lincosamides and streptogramins	
<i>J01FA</i>	<i>Macrolides</i>	
J01FA01	erythromycin	6.2.2
J01FA10	azithromycin	6.2.2
<i>J01FF</i>	<i>Lincosamides</i>	
J01FF01	clindamycin	6.2.2
J01G	Aminoglycoside antibacterials	
<i>J01GA</i>	<i>Streptomycins</i>	
J01GA01	streptomycin	6.2.4
<i>J01GB</i>	<i>Other aminoglycosides</i>	
J01GB03	gentamicin	6.2.2
J01GB04	kanamycin	6.2.4
J01GB06	amikacin	6.2.4
J01M	Quinolone antibacterials	
<i>J01MA</i>	<i>Fluoroquinolones</i>	
J01MA01	ofloxacin	6.2.4
J01MA02	ciprofloxacin	6.2.2
J01MA12	levofloxacin	6.2.4
J01X	Other antibacterials	
<i>J01XA</i>	<i>Glycopeptide antibacterials</i>	
J01XA01	vancomycin	6.2.2
<i>J01XD</i>	<i>Imidazole derivatives</i>	
J01XD01	metronidazole	6.2.2
<i>J01XE</i>	<i>Nitrofurantoin derivatives</i>	
J01XE01	nitrofurantoin	6.2.2
<i>J01XX</i>	<i>Other antibacterials</i>	
J01XX04	spectinomycin	6.2.2
J02	Antimycotics for systemic use	
J02A	Antimycotics for systemic use	
<i>J02AA</i>	<i>Antibiotics</i>	
J02AA01	amphotericin B	6.3; 6.5.2

ATC code	ATC group/medicine or item	Section
J02AC	Triazole derivatives	
<i>J02AC01</i>	<i>fluconazole</i>	6.3
J02AX	Other antimycotics for systemic use	
<i>J02AX01</i>	flucytosine	6.3
J04	Antimycobacterials	
J04A	Drugs for treatment of tuberculosis	
<i>J04AA</i>	<i>Aminosalicylic acid and derivatives</i>	
<i>J04AA01</i>	p-aminosalicylic acid*	6.2.4
<i>J04AB</i>	<i>Antibiotics</i>	
<i>J04AB01</i>	cycloserine	6.2.4
<i>J04AB02</i>	rifampicin	6.2.3; 6.2.4
<i>J04AB30</i>	capreomycin	6.2.4
<i>J04AC</i>	<i>Hydrazides</i>	
<i>J04AC01</i>	isoniazid	6.2.4
<i>J04AD</i>	<i>Thiocarbamide derivatives</i>	
<i>J04AD03</i>	ethionamide	6.2.4
<i>J04AK</i>	<i>Other drugs for treatment of tuberculosis</i>	
<i>J04AK01</i>	pyrazinamide	6.2.4
<i>J04AK02</i>	ethambutol	6.2.4
<i>J04AM</i>	<i>Combinations of drugs for treatment of tuberculosis</i>	
<i>J04AM02</i>	rifampicin + isoniazid*	6.2.4
<i>J04AM03</i>	isoniazid + ethambutol*	6.2.4
<i>J04AM05</i>	rifampicin + isoniazid + pyrazinamide*	6.2.4
<i>J04AM06</i>	rifampicin + isoniazid + pyrazinamide + ethambutol*	6.2.4
	rifampicin + isoniazid + ethambutol	6.2.4
J04B	Drugs for treatment of lepra	
<i>J04BA</i>	<i>Drugs for treatment of lepra</i>	
<i>J04BA01</i>	clofazimine	6.2.3
<i>J04BA02</i>	dapsone	6.2.3
J05	Antivirals for systemic use	
J05A	Direct acting antivirals	
<i>J05AB</i>	<i>Nucleosides and nucleotides excl. reverse transcriptase inhibitors</i>	
<i>J05AB01</i>	aciclovir	6.4.1
<i>J05AB04</i>	ribavirin	6.4.3
<i>J05AE</i>	<i>Protease inhibitors</i>	
<i>J05AE01</i>	saquinavir (SQV)	6.4.2.3
<i>J05AE02</i>	indinavir (IDV)	6.4.2.3
<i>J05AE03</i>	ritonavir (r)	6.4.2.3
<i>J05AE04</i>	nelfinavir (NFV)	6.4.2.3
<i>J05AE30</i>	lopinavir + ritonavir (LPV/r)*	6.4.2.3

ATC code	ATC group/medicine or item	Section
<i>J05AF</i>	<i>Nucleoside reverse transcriptase inhibitors</i>	
J05AF01	zidovudine (ZDV or AZT)	6.4.2.1
J05AF02	didanosine (ddl)	6.4.2.1
J05AF04	stavudine (d4T)	6.4.2.1
J05AF05	lamivudine (3TC)	6.4.2.1
J05AF06	abacavir (ABC)	6.4.2.1
J05AF07	tenofovir	6.4.2.1
J05AF09	emtricitabine	6.4.2.1
<i>J05AG</i>	<i>Non-nucleoside reverse transcriptase inhibitors</i>	
J05AG01	nevirapine (NVP)	6.4.2.2
J05AG03	efavirenz (EFV or EFZ)	6.4.2.2
<i>J05AGR</i>		
J05AR01	zidovudine (ZDV or AZT) + lamivudine	
J05AR03	emtricitabine + tenofovir	
J05AR05	zidovudine + lamivudine + nevirapine	
J05AR06	efavirenz + emtricitabine + tenofovir stavudine + lamivudine + nevirapine	
J06	Immune sera and immunoglobulins	
J06A	Immune sera	
<i>J06AA</i>	<i>Immune sera</i>	
J06AA01	diphtheria antitoxin	19.2
J06AA03	antivenom immunoglobulin*	19.2
J06B	Immunoglobulins	
<i>J06BA</i>	<i>Immunoglobulins, normal human</i>	
J06BA01	immunoglobulins, normal human, for extravascular adm	19.2
J06BA02	immunoglobulins, normal human, for intravascular adm	19.2
<i>J06BB</i>	<i>Specific immunoglobulins</i>	
J06BB01	anti-D immunoglobulin (human)	19.2
J06BB02	antitetanus immunoglobulin (human)	19.2
J06BB05	rabies immunoglobulin	19.2
J07	Vaccines	
J07A	Bacterial vaccines	
<i>J07AE</i>	<i>Cholera vaccines</i>	
J07AE	cholera vaccine	19.3
<i>J07AH</i>	<i>Meningococcal vaccines</i>	
J07AH	meningococcal meningitis vaccine*	19.3
<i>J07AJ</i>	<i>Pertussis vaccines</i>	
J07AJ51	diphtheria-pertussis-tetanus vaccine*	19.3
<i>J07AM</i>	<i>Tetanus vaccines</i>	
J07AM51	diphtheria-tetanus vaccine*	19.3

ATC code	ATC group/medicine or item	Section
<i>J07AN</i>	<i>Tuberculosis vaccines</i>	
J07AN01	BCG vaccine*	19.3
<i>J07AP</i>	<i>Typhoid vaccines</i>	
J07AP	typhoid vaccine	19.3
J07B	Viral vaccines	
<i>J07BB</i>	<i>Influenza vaccines</i>	
J07BB	influenza vaccine	19.3
<i>J07BC</i>	<i>Hepatitis vaccines</i>	
J07BC01	hepatitis B vaccine	19.3
<i>J07BD</i>	<i>Measles vaccine*</i>	
J07BD52	measles-mumps-rubella vaccine*	19.3
<i>J07BF</i>	<i>poliomyelitis vaccine</i>	19.3
<i>J07BG</i>	<i>rabies vaccine</i>	19.3
<i>J07BJ</i>	<i>rubella vaccine</i>	19.3
<i>J07BL</i>	<i>yellow fever vaccine</i>	19.3
L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	
L01	Antineoplastic agents	
L01A	Alkylating agents	
<i>L01AA</i>	<i>Nitrogen mustard analogues</i>	
L01AA01	cyclophosphamide	8.2
L01AA02	chlorambucil	8.2
<i>L01AX</i>	<i>Other alkylating agents</i>	
L01AX04	dacarbazine	8.2
L01B	Antimetabolites	
<i>L01BA</i>	<i>Folic acid analogues</i>	
L01BA01	methotrexate	2.4; 8.2
<i>L01BB</i>	<i>Purine analogues</i>	
L01BB02	mercaptopurine	8.2
<i>L01BC</i>	<i>Pyrimidine analogues</i>	
L01BC01	cytarabine	8.2
L01BC02	fluorouracil	8.2; 13.5
L01C	Plant alkaloids and other natural products	
<i>L01CA</i>	<i>Vinca alkaloids and analogues</i>	
L01CA01	vinblastine	8.2
L01CA02	vincristine	8.2
<i>L01CB</i>	<i>Podophyllotoxin derivatives</i>	
L01CB01	etoposide	8.2

ATC code	ATC group/medicine or item	Section
L01D	Cytotoxic antibiotics and related substances	
<i>L01DA</i>	<i>Actinomycines</i>	
L01DA01	dactinomycin	8.2
<i>L01DB</i>	<i>Anthracyclines and related substances</i>	
L01DB01	doxorubicin	8.2
L01DB02	daunorubicin	8.2
<i>L01DC</i>	<i>Other cytotoxic antibiotics</i>	
L01DC01	bleomycin	8.2
L01X	Other antineoplastic agents	
<i>L01XA</i>	<i>Platinum compounds</i>	
L01XA01	cisplatin	8.2
<i>L01XB</i>	<i>Methylhydrazines</i>	
L01XB01	procarbazine	8.2
<i>L01XX</i>	<i>Other antineoplastic agents</i>	
L01XX02	asparaginase	8.2
L02	Endocrine therapy	
L02B	Hormone antagonists and related agents	
<i>L02BA</i>	<i>Anti-estrogens</i>	
L02BA01	tamoxifen	8.3
L04	Immunosuppressive agents	
L04A	Immunosuppressive agents	
<i>L04AA</i>	<i>Selective immunosuppressive agents</i>	
L04AA01	ciclosporin	8.1
<i>L04AX</i>	<i>Other immunosuppressive agents</i>	
L04AX01	azathioprine	2.4; 8.1
M	MUSCULO-SKELETAL SYSTEM	
M01	Antiinflammatory and antirheumatic products	
M01A	Antiinflammatory and antirheumatic products, non-steroids	
<i>M01AE</i>	<i>Propionic acid derivatives</i>	
M01AE01	ibuprofen	2.1
M01C	Specific antirheumatic agents	
<i>M01CC</i>	<i>Penicillamine and similar agents</i>	
M01CC01	penicillamine	2.4; 4.2
M03	Muscle relaxants	
M03A	Muscle relaxants, peripherally acting agents	
<i>M03AA</i>	<i>Curare alkaloids</i>	
M03AA01	alcuronium	20
<i>M03AB</i>	<i>Choline derivatives</i>	
M03AB01	suxamethonium	20

ATC code	ATC group/medicine or item	Section
M03AC	<i>Other quaternary ammonium compounds</i>	
M03AC03	vecuronium	20
M04	Antigout preparations	
M04A	Antigout preparations	
M04AA	<i>Preparations inhibiting uric acid production</i>	
M04AA01	allopurinol	2.3
N	NERVOUS SYSTEM	
N01	Anesthetics	
N01A	Anesthetics, general	
N01AB	<i>Halogenated hydrocarbons</i>	
N01AB01	halothane	1.1
N01AF	<i>Barbiturates, plain</i>	
N01AF03	thiopental	1.1
N01AX	<i>Other general anesthetics</i>	
N01AX03	ketamine	1.1
N01AX13	nitrous oxide	1.1
N01B	Anesthetics, local	
N01BB	<i>Amides</i>	
N01BB01	bupivacaine	1.2
N01BB02	lidocaine	1.2
N01BB52	lidocaine + epinephrine (adrenaline)*	1.2
N02	Analgesics	
N02A	Opioids	
N02AA	<i>Natural opium alkaloids</i>	
N02AA01	morphine	1.3; 2.2
N02B	Other analgesics and antipyretics	
N02BA	<i>Salicylic acid and derivatives</i>	
N02BA01	acetylsalicylic acid	2.1; 7.1
N02BE	<i>Anilides</i>	
N02BE01	paracetamol	2.1; 7.1
N03	Antiepileptics	
N03A	Antiepileptics	
N03AA	<i>Barbiturates and derivatives</i>	
N03AA02	phenobarbital	5
N03AB	<i>Hydantoin derivatives</i>	
N03AB02	phenytoin	5
N03AD	<i>Succinimide derivatives</i>	
N03AD01	ethosuximide	5
N03AF	<i>Carboxamide derivatives</i>	
N03AF01	carbamazepine	5; 24.2.2

ATC code	ATC group/medicine or item	Section
N03AG	<i>Fatty acid derivatives</i>	
N03AG01	valproic acid	5; 24.2.2
N04	Anti-parkinson drugs	
N04A	Anticholinergic agents	
N04AA	<i>Tertiary amines</i>	
N04AA02	biperiden	9
N04B	Dopaminergic agents	
N04BA	<i>Dopa and dopa derivatives</i>	
N04BA02	levodopa + carbidopa*	9
N05	Psycholeptics	
N05A	Antipsychotics	
N05AA	<i>Phenothiazines with aliphatic side-chain</i>	
N05AA01	chlorpromazine	24.1
N05AB	<i>Phenothiazines with piperazine structure</i>	
N05AB02	fluphenazine	24.1
N05AD	Butyrophenone derivatives	
N05AD01	haloperidol	24.1
N05AN	<i>Lithium</i>	
N05AN01	lithium carbonate*	24.2.2
N05B	Anxiolytics	
N05BA	<i>Benzodiazepine derivatives</i>	
N05BA01	diazepam	1.3; 5; 24.3
N06	Psychoanaleptics	
N06A	Antidepressants	
N06AA	<i>Non-selective monoamine reuptake inhibitors</i>	
N06AA04	clomipramine	24.4
N06AA09	amitriptyline	24.2.1
N06AB	<i>Selective serotonin reuptake inhibitors</i>	
N06AB03	fluoxetine	24.2.1
N06B	Psychostimulants, agents used for ADHD and nootropics	
N06BC	<i>Xanthine derivatives</i>	
N06BC01	caffeine citrate	25.2
N07	Other nervous system drugs	
N07A	Parasympathomimetics	
N07AA	<i>Anticholinesterases</i>	
N07AA01	neostigmine	20
N07AA02	pyridostigmine	20
N07B	Drugs used in addictive disorders	
N07BC	<i>Drugs used in opioid dependence</i>	
N07BC02	methadone	24.5

ATC code	ATC group/medicine or item	Section
P	ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	
P01	Antiprotozoals	
P01A	Agents against amoebiasis and other protozoal diseases	
<i>P01AB</i>	<i>Nitroimidazole derivatives</i>	
P01AB01	metronidazole	6.5.1
<i>P01AC</i>	<i>Dichloroacetamide derivatives</i>	
P01AC01	diloxanide	6.5.1
P01B	Antimalarials	
<i>P01BA</i>	<i>Aminoquinolines</i>	
P01BA01	chloroquine	2.4; 6.5.3.1; 6.5.3.2
P01BA03	primaquine	6.5.3.1
P01BA06	amodiaquine	6.5.3.1
<i>P01BB</i>	<i>Biguanides</i>	
P01BB01	proguanil	6.5.3.2
<i>P01BC</i>	<i>Methanolquinolines</i>	
P01BC01	quinine	6.5.3.1
P01BC02	mefloquine	6.5.3.1; 6.5.3.2
<i>P01BD</i>	<i>Diaminopyrimidines</i>	
P01BD01	pyrimethamine	6.5.4
P01BD51	sulfadoxine + pyrimethamine*	6.5.3.1
<i>P01BE</i>	<i>Artemisinin and derivatives</i>	
P01BE02	artemether	6.5.3.1
P01BE03	artesunate	6.5.3.1
P01BE52	artemether + lumefantrine*	6.5.3.1
P01C	Agents against leishmaniasis and trypanosomiasis	
<i>P01CA</i>	<i>Nitroimidazole derivatives</i>	
P01CA02	benznidazole	6.5.5.2
<i>P01CB</i>	<i>Antimony compounds</i>	
P01CB01	meglumine antimoniate	6.5.2
<i>P01CC</i>	<i>Nitrofurans derivatives</i>	
P01CC01	nifurtimox	6.5.5.2
<i>P01CD</i>	<i>Arsenic compounds</i>	
P01CD01	melarsoprol	6.5.5.1
<i>P01CX</i>	<i>Other agents against leishmaniasis and trypanosomiasis</i>	
P01CX01	pentamidine*	6.5.2; 6.5.4; 6.5.5.1
P01CX02	suramin sodium	6.1.2; 6.5.5.1
P01CX03	eflornithine	6.5.5.1

ATC code	ATC group/medicine or item	Section
P02	Anthelmintics	
P02B	Antitrepatodals	
<i>P02BA</i>	<i>Quinoline derivatives and related substances</i>	
P02BA01	praziquantel	6.1.1; 6.1.3
P02BA02	oxamniquine	6.1.3
P02BX	Other antitrepatodal agents	
P02BX04	triclabendazole	6.1.3
P02C	Antinematodal agents	
P02CA	Benzimidazole derivatives	
P02CA01	mebendazole	6.1.1
P02CA03	albendazole	6.1.1
P02CB	Piperazine and derivatives	
P02CB02	diethylcarbamazine	6.1.2
<i>P02CC</i>	<i>Tetrahydropyrimidine derivatives</i>	
P02CC01	pyrantel	6.1.1
<i>P02CE</i>	<i>Imidazothiazole derivatives</i>	
P02CE01	levamisole	6.1.1
<i>P02CF</i>	<i>Avermectines</i>	
P02CF01	ivermectin	6.1.2
P02D	Anticestodals	
<i>P02DA</i>	<i>Salicylic acid derivatives</i>	
P02DA01	niclosamide	6.1.1
P03	Ectoparasiticides, incl. scabicides, insecticides and repellents	
P03A	Ectoparasiticides, incl. scabicides	
<i>P03AC</i>	<i>Pyrethrines, incl. synthetic compounds</i>	
P03AC04	permethrin	13.6
<i>P03AX</i>	<i>Other ectoparasiticides, incl. scabicides</i>	
P03AX01	benzyl benzoate	13.6
R	RESPIRATORY SYSTEM	
R03	Drugs for obstructive airway diseases	
<i>R03A</i>	<i>Adrenergics, inhalants</i>	
<i>R03AC</i>	<i>Selective beta-2-adrenoreceptor agonists</i>	
R03AC02	salbutamol	25.1
R03B	Other drugs for obstructive airway diseases, inhalants	
<i>R03BA</i>	<i>Glucocorticoids</i>	
R03BA01	beclometasone	25.1
<i>R03BB</i>	<i>Anticholinergics</i>	
R03BB01	ipratropium bromide	25.1

ATC code	ATC group/medicine or item	Section
R03C	Adrenergics for systemic use	
<i>R03CA</i>	<i>Alpha- and beta-adrenoreceptor agonists</i>	
R03CA02	ephedrine	1.2
<i>R03CC</i>	<i>Selective beta-2-adrenoreceptor agonists</i>	
R03CC02	salbutamol	25.1
R05	Cough and cold preparations	
R05D	Cough suppressants, excl. combinations with expectorants	
<i>R05DA</i>	<i>Opium alkaloids and derivatives</i>	
R05DA04	codeine	2.2; 17.5.3
R06	Antihistamines for systemic use	
R06A	Antihistamines for systemic use	
<i>R06AB</i>	<i>Substituted alkylamines</i>	
R06AB04	chlorphenamine	3
<i>R06AD</i>	<i>Phenothiazine derivatives</i>	
R06AD02	promethazine	1.3; 17.2
S	SENSORY ORGANS	
S01	Ophthalmologicals	
S01A	Antiinfectives	
<i>S01AA</i>	<i>Antibiotics</i>	
S01AA09	tetracycline	21.1
S01AA11	gentamicin	21.1
<i>S01AD</i>	<i>Antivirals</i>	
S01AD03	aciclovir	21.1
S01B	Antiinflammatory agents	
<i>S01BA</i>	<i>Corticosteroids, plain</i>	
S01BA04	prednisolone	21.2
S01E	Antiglaucoma preparations and miotics	
<i>S01EA</i>	<i>Sympathomimetics in glaucoma therapy</i>	
S01EA01	epinephrine	21.5
<i>S01EB</i>	<i>Parasympathomimetics</i>	
S01EB01	pilocarpine	21.4
<i>S01EC</i>	<i>Carbonic anhydrase inhibitors</i>	
S01EC01	acetazolamide	21.4
<i>S01ED</i>	<i>Beta blocking agents</i>	
S01ED01	timolol	21.4
S01F	Mydriatics and cycloplegics	
<i>S01FA</i>	<i>Anticholinergics</i>	
S01FA01	atropine	21.5
S01FA06	tropicamide	14.1

ATC code	ATC group/medicine or item	Section
S01H	Local anesthetics	
<i>S01HA</i>	<i>Local anesthetics</i>	
S01HA03	tetracaine	21.3
S01J	Diagnostic agents	
<i>S01JA</i>	<i>Colouring agents</i>	
S01JA01	fluorescein	14.1
V	VARIOUS	
V03	All other therapeutic products	
V03A	All other therapeutic products	
<i>V03AB</i>	<i>Antidotes</i>	
V03AB03	sodium calcium edetate*	4.2
V03AB06	sodium thiosulfate*	4.2; 13.1
V03AB08	sodium nitrite	4.2
V03AB09	dimercaprol	4.2
V03AB14	protamine sulfate*	10.2
V03AB15	naloxone	4.2
V03AB17	methylthionium chloride (methylene blue)	4.2
V03AB23	acetylcysteine	4.2
V03AB26	DL-methionine*	4.2
V03AB31	potassium ferric hexacyanoferrate (II) · 2H ₂ O (Prussian blue)	4.2
<i>V03AC</i>	<i>Iron chelating agents</i>	
V03AC01	deferoxamine	4.2
V03AF	Detoxifying agents for antineoplastic treatment	
<i>V03AF03</i>	<i>calcium folinate</i>	8.2
<i>V03AN</i>	<i>Medical gases</i>	
V03AN	oxygen	1.1
V04	Diagnostic agents	
V04C	Other diagnostic agents	
<i>V04CF</i>	<i>Tuberculosis diagnostics</i>	
V04CF01	tuberculin, purified protein derivative (PPD)*	19.1
V07	All other non-therapeutic products	
V07A	All other non-therapeutic products	
<i>V07AB</i>	<i>Solvents and diluting agents, incl. irrigating solutions</i>	
V07AB	water for injection*	26.3
V07AV	Technical disinfectants	
V07AV	glutaral	15.2
V08	Contrast media	
V08A	X-ray contrast media, iodinated	
<i>V08AA</i>	<i>Watersoluble, nephrotropic, high osmolar X-ray contrast media</i>	
V08AA01	amidotrizoate*	14.2

ATC code	ATC group/medicine or item	Section
V08AB	<i>Watersoluble, nephrotropic, low osmolar X-ray contrast media</i>	
V08AB02	iohexol	14.2
V08AC	<i>Watersoluble, hepatotropic X-ray contrast media</i>	
V08AC02	meglumine iotroxate*	14.2
V08B	X-ray contrast media, non-iodinated	
V08BA	<i>Barium sulfate containing X-ray contrast media</i>	
V08BA01	barium sulfate*	14.2

* Medicine or item name differs slightly from the name used.

Annex 4

Alphabetical list of essential medicines (with ATC classification code numbers)

ATC group/medicine or item	ATC code	section
abacavir (ABC)	J05AF06	6.4.2.1
acetazolamide	S01EC01	21.4
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	B01AC06	12.5
acetylsalicylic acid	N02BA01	2.1; 7.1
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
albendazole	P02CA03	6.1.1
alcuronium	M03AA01	20
allopurinol	M04AA01	2.3
aluminium diacetate	D10AX05	13.4
aluminium hydroxide	A02AB01	17.1
amidotrizoate*	V08AA01	14.2
amikacin	J01GB06	6.2.4
amiloride	C03DB01	16
amitriptyline	N06AA09	24.2.1
amlodipine	C08CA01	12.3
amodiaquine	P01BA06	6.5.3.1
amoxicillin	J01CA04	6.2.1
amoxicillin + clavulanic acid*	J01CR02	6.2.1
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
anti-D immunoglobulin (human)	J06BB01	19.2
antitetanus immunoglobulin (human)	J06BB02	19.2
antivenom immunoglobulin*	J06AA03	19.2
artemether	P01BE02	6.5.3.1
artemether + lumefantrine*	P01BE52	6.5.3.1
artesunate	P01BE03	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2
atenolol	C07AB03	12.1;12.2;12.3
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	2.4; 8.1
azithromycin	J01FA10	6.2.2
barium sulfate*	V08BA01	14.2
BCG vaccine*	J07AN01	19.3
beclometasone	R03BA01	25.1

ATC group/medicine or item	ATC code	section
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	P01CA02	6.5.5.2
benzoic acid + salicylic acid*	D01AE20	13.1
benzoyl peroxide	D10AE01	13.5
benzyl benzoate	P03AX01	13.6
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
biperiden	N04AA02	9
bleomycin	L01DC01	8.2
bupivacaine	N01BB01	1.2
caffeine citrate	N06BC01	25.2
calamine lotion*	D02AB	13.3
calcium folinate	V03AF03	8.2
calcium gluconate	A12AA03	4.2; 27
capreomycin	J04AB30	6.2.4
carbamazepine	N03AF01	5; 24.2.2
cefazolin	J01DB04	6.2.1
cefixime	J01DD08	6.2.1
ceftazidime	J01DD02	6.2.1
ceftriaxone	J01DD04	6.2.1
charcoal, activated*	A07BA01	4.1
chlorambucil	L01AA02	8.2
chloramphenicol	J01BA01	6.2.2
chlorhexidine	D08AC02	15.1
chlorine base compound*	D08AX	15.2
chloroquine	P01BA01	2.4; 6.5.3.1; 6.5.3.2
chloroxylenol	D08AE05	15.2
chlorphenamine	R06AB04	3
chlorpromazine	N05AA01	24.1
cholera vaccine	J07AE	19.3
ciclosporin	L04AA01	8.1
ciprofloxacin	J01MA02	6.2.2
cisplatin	L01XA01	8.2
clindamycin	J01FF01	6.2.2
clofazimine	J04BA01	6.2.3
clomifene	G03GB02	18.6
clomipramine	N06AA04	24.4
clotrimazole	G01AF02	6.3
cloxacillin	J01CF02	6.2.1
coal tar*	D05AA	13.5
codeine	R05DA04	2.2; 17.5.3
copper-containing device*	G02BA02	18.3.3
cyclophosphamide	L01AA01	8.2
cycloserine	J04AB01	6.2.4
cytarabine	L01BC01	8.2

ATC group/medicine or item	ATC code	section
dacarbazine	L01AX04	8.2
dactinomycin	L01DA01	8.2
dapsone	J04BA02	6.2.3
daunorubicin	L01DB02	8.2
deferoxamine	V03AC01	4.2
dexamethasone	H02AB02	3; 8.3
dextran 70*	B05AA05	11.1
diaphragms*	G02BB	18.3.4
diazepam	N05BA01	1.3; 5; 24.3
didanosine (ddI)	J05AF02	6.4.2.1
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.2; 12.4
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria-pertussis-tetanus vaccine*	J07AJ51	19.3
diphtheria-tetanus vaccine*	J07AM51	19.3
dithranol	D05AC01	13.5
DL-methionine*	V03AB26	4.2
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2
doxycycline	J01AA02	6.2.2; 6.5.3.1; 6.5.3.2
efavirenz (EFV or EFZ)	J05AG03	6.4.2.2
efavirenz + emtricitabine + tenofovir	J05AR06	
eflornithine	P01CX03	6.5.5.1
emtricitabine	J05AF09	6.4.2.1
emtricitabine + tenofovir	J05AR03	
enalapril	C09AA02	12.3; 12.4
ephedrine	R03CA02	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 12.2; 25.1
ergocalciferol	A11CC01	27
ergometrine	G02AB03	22.1
erythromycin	J01FA01	6.2.2
ethambutol	J04AK02	6.2.4
ethanol	D08AX08	15.1
ethinylestradiol	G03CA01	18.4
ethinylestradiol + levonorgestrel*	G03AB03	18.3.1
ethinylestradiol + norethisterone*	G03AA05	18.3.1
ethionamide	J04AD03	6.2.4
ethosuximide	N03AD01	5
etoposide	L01CB01	8.2
factor IX complex (coagulation factors II, VII, IX, X) concentrate*	B02BD01	11.2

ATC group/medicine or item	ATC code	section
factor VIII concentrate*	B02BD02	11.2
ferrous salt*	B03A	10.1
ferrous salt + folic acid*	B03AD	10.1
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fluorescein	S01JA01	14.1
fluorouracil	L01BC02	8.2; 13.5
fluoxetine	N06AB03	24.2.1
fluphenazine	N05AB02	24.1
folic acid	B03BB01	10.1
furosemide	C03CA01	12.4; 16
gentamicin	J01GB03	6.2.2
gentamicin	S01AA11	21.1
glibenclamide	A10BB01	18.5
glucose		26.2
glucose with sodium chloride*	B05BB02	26.2
glutaral	V07AV	15.2
glyceryl trinitrate	C01DA02	12.1
griseofulvin	D01BA01	6.3
haloperidol	N05AD01	24.1
halothane	N01AB01	1.1
heparin sodium*	B01AB01	10.2
hepatitis B vaccine	J07BC01	19.3
human normal immunoglobulin		11.2
hydrazaline	C02DB02	12.3
hydrochlorothiazide	C03AA03	12.3; 12.4; 16
hydrocortisone	A07EA02	17.3
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.3
hydroxocobalamin	B03BA03	10.1
ibuprofen	M01AE01	2.1
imipenem + cilastatin*	J01DH51	6.2.1
indinavir (IDV)	J05AE02	6.4.2.3
influenza vaccine	J07BB	19.3
insulin injection (soluble)*	A10AB	18.5
insulin, intermediate-acting*	A10AC	18.5
intraperitoneal dialysis solution*	B05DA	23
iodine*	A12CX	27
iohexol	V08AB02	14.2
ipratropium bromide	R03BB01	25.1
isoniazid	J04AC01	6.2.4
isoniazid + ethambutol*	J04AM03	6.2.4
isosorbide dinitrate	C01DA08	12.1
ivermectin	P02CF01	6.1.2

ATC group/medicine or item	ATC code	section
kanamycin	J01GB04	6.2.4
ketamine	N01AX03	1.1
lamivudine (3TC)	J05AF05	6.4.2.1
levamisole	P02CE01	6.1.1
levodopa + carbidopa*	N04BA02	9
levofloxacin	J01MA12	6.2.4
levonorgestrel	G03AC03	18.3.1
levonorgestrel-releasing implant		18.3.5
levothyroxine*	H03AA01	18.8
lidocaine	C01BB01	12.2
lidocaine	N01BB02	1.2
lidocaine + epinephrine (adrenaline)*	N01BB52	1.2
lithium carbonate*	N05AN01	24.2.2
lopinavir + ritonavir (LPV/r)*	J05AE30	6.4.2.3
magnesium hydroxide	A02AA04	17.1
magnesium sulfate	B05XA05	5
mannitol	B05BC01	16
measles-mumps-rubella vaccine*	J07BD52	19.3
mebendazole	P02CA01	6.1.1
medroxyprogesterone acetate*	G03AC06	18.3.2; 18.7
medroxyprogesterone + estradiol cypionate	G03AA08	18.3.2
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
meglumine iotroxate*	V08AC02	14.2
melarsoprol	P01CD01	6.5.5.1
meningococcal meningitis vaccine*	J07AH	19.3
mercaptopurine	L01BB02	8.2
metformin	A10BA02	18.5
methadone	N07BC02	24.5
methotrexate	L01BA01	2.4; 8.2
methyl dopa*	C02AB01	12.3
methylrosanilinium chloride (gentian violet)*	D01AE02	13.2
methylthioninium chloride (methylene blue)	V03AB17	4.2
metoclopramide	A03FA01	17.2
metronidazole	J01XD01	6.2.2
metronidazole	P01AB01	6.5.1
miconazole	D01AC02	13.1
mifepristone	G03XB01	22.1
misoprostol	A02BB01	22.1
morphine	N02AA01	1.3; 2.2
naloxone	V03AB15	4.2
nefinavir (NFV)	J05AE04	6.4.2.3
neomycin + bacitracin*	D06AX04	13.2
neostigmine	N07AA01	20
nevirapine (NVP)	J05AG01	6.4.2.2

ATC group/medicine or item	ATC code	section
niclosamide	P02DA01	6.1.1
nicotinamide	A11HA01	27
nifedipine	C08CA05	22.2
nifurtimox	P01CC01	6.5.5.2
nitrofurantoin	J01XE01	6.2.2
nitrous oxide	N01AX13	1.1
norethisterone	G03DC02	18.7
norethisterone enantate*	G03AC01	18.3.2
nystatin	A07AA02	6.3
nystatin	D01AA01	6.3
nystatin	G01AA01	6.3
ofloxacin	J01MA01	6.2.4
oral rehydration salts*	A07CA	17.5.1; 26.1
oxamiquine	P02BA02	6.1.3
oxygen	V03AN	1.1
oxytocin	H01BB02	22.1
p-aminosalicylic acid*	J04AA01	6.2.4
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
penicillamine	M01CC01	2.4; 4.2
pentamidine*	P01CX01	6.5.2; 6.5.4; 6.5.5.1
permethrin	P03AC04	13.6
phenobarbital	N03AA02	5
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pilocarpine	S01EB01	21.4
podophyllum resin*	D06BB04	13.5
poliomyelitis vaccine	J07BF	19.3
polygeline*	B05AA06	11.1
polyvidone iodine	D08AG02	15.1
potassium chloride	B05XA01	26.1; 26.2
potassium ferric hexacyanoferrate (II).2H ₂ O (Prussian blue)	V03AB31	4.2
potassium iodide*	H03CA	6.3; 18.8
potassium permanganate	D08AX06	13.2
praziquantel	P02BA01	6.1.1; 6.1.3
prednisolone	H02AB06	3; 8.3
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1
procainamide	C01BA02	12.2
procaine benzylpenicillin*	J01CE09	6.2.1
procarbazine	L01XB01	8.2
proguanil	P01BB01	6.5.3.2
promethazine	R06AD02	1.3; 17.2
propranolol	C07AA05	7.2

ATC group/medicine or item	ATC code	section
propylthiouracil	H03BA02	18.8
protamine sulfate*	V03AB14	10.2
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.4
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
quinidine	C01BA01	12.2
quinine	P01BC01	6.5.3.1
rabies immunoglobulin	J06BB05	19.2
rabies vaccine	J07BG	19.3
ranitidine	A02BA02	17.1
retinol	A11CA01	27
ribavirin	J05AB04	6.4.3
riboflavin	A11HA04	27
rifampicin	J04AB02	6.2.3; 6.2.4
rifampicin + isoniazid*	J04AM02	6.2.4
rifampicin + isoniazid + ethambutol		6.2.4
rifampicin + isoniazid + pyrazinamide*	J04AM05	6.2.4
rifampicin + isoniazid + pyrazinamide + ethambutol*	J04AM06	6.2.4
ritonavir (r)	J05AE03	6.4.2.3
rubella vaccine	J07BJ	19.3
salbutamol	R03AC02	25.1
salbutamol	R03CC02	25.1
salicylic acid	D01AE12	13.5
saquinavir (SQV)	J05AE01	6.4.2.3
selenium sulfide	D01AE13	13.1
senna*	A06AB06	17.4
silver sulfadiazine	D06BA01	13.2
simvastatin	C01AA01	12.6
sodium calcium edetate*	V03AB03	4.2
sodium chloride	B05XA03	26.2
sodium fluoride	A12CD01	27
sodium hydrogen carbonate*	B05XA02	26.2
sodium lactate, compound solution*	B05BB01	26.2
sodium nitrite	V03AB08	4.2
sodium nitroprusside*	C02DD01	12.3
sodium thiosulfate*	V03AB06	4.2; 13.1
spectinomycin	J01XX04	6.2.2
spironolactone	C03DA01	16
stavudine (d4T)	J05AF04	6.4.2.1
stavudine + lamivudine + nevirapine		
streptokinase	B01AD01	12.5
streptomycin	J01GA01	6.2.4
sulfadiazine	J01EC02	6.2.2

ATC group/medicine or item	ATC code	section
sulfadoxine + pyrimethamine*	P01BD51	6.5.3.1
sulfamethoxazole + trimethoprim	J01EE01	6.2.2; 6.5.4
sulfasalazine	A07EC01	2.4; 17.3
suramin sodium	P01CX02	6.1.2; 6.5.5.1
suxamethonium	M03AB01	20
tamoxifen	L02BA01	8.3
tenofovir	J05AF07	6.4.2.1
testosterone	G03BA03	18.2
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thiamine	A11DA01	27
thiopental	N01AF03	1.1
timolol	S01ED01	21.4
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.2
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD)*	V04CF01	19.1
typhoid vaccine	J07AP	19.3
urea*	D02AE01	13.5
valproic acid	N03AG01	5; 24.2.2
vancomycin	J01XA01	6.2.2
vecuronium	M03AC03	20
verapamil	C08DA01	12.1; 12.2
vinblastine	L01CA01	8.2
vincristine	L01CA02	8.2
warfarin	B01AA03	10.2
water for injection*	V07AB	26.3
yellow fever vaccine	J07BL	19.3
zidovudine (ZDV or AZT)	J05AF01	6.4.2.1
zidovudine (ZDV or AZT) + lamivudine	J05AR01	
zidovudine + lamivudine + nevirapine	J05AR05	
zinc sulfate	A12CB01	17.5.2

* Medicine or item name differs slightly from the name used.

Annex 5

Proposed procedure to update and disseminate the WHO Model List of Essential Medicines¹

Document EB109/8 (Annex), 7 December 2001

WHO Expert Committee on the Use of Essential Drugs
Applications for inclusion, change or deletion
Review of applications and draft recommendations
Criteria for the selection of essential medicines
Presentation of recommendations, report of the Expert Committee
WHO Essential Medicines Library

WHO Expert Committee on the Use of Essential Drugs

1. The Model List is drawn up by the WHO Expert Committee on the Use of Essential Drugs, following the Regulations for Expert Advisory Panels and Committees.² Since 1977 the Expert Committee has been convened every two years, but could meet more often if needed.
2. The Expert Committee comprises eight to 12 members drawn from the WHO Expert Advisory Panels³ for Drug Evaluation and for Drug Policies and Management, and, where appropriate and in consultation with the relevant department, from other expert advisory panels. Expert Committee members are selected by the Director-General to represent a wide range of geographical and professional backgrounds, including clinical pharmacology, clinical medicine, international public health, guideline development methodology, systematic literature search methods, risk-assessment and cost-effectiveness analysis.
3. Meetings of the Expert Committee are private and members are required to sign a confidentiality undertaking and complete a WHO declaration of interest form before the meeting. Observers may be invited in accordance with Regulations for Expert Advisory Panels and Committees to attend all or parts of the meetings of the Expert Committee. Patient advocacy groups and representatives of the health care industry are invited to comment on the applications and draft recommendations (see below),

¹ As part of the revised procedure for updating the Model List, the term "essential medicines" is used in preference to "essential drugs". This reflects the common use of the term "medicines" to describe pharmaceutical preparations used in clinical health care practice.

² *WHO Basic Documents*, 43rd ed., 2001, pp.101–109.

³ Members of Expert Advisory Panels are proposed by WHO and, when approved by their respective government, appointed for one or more periods of up to four years.

but are not invited to attend decision-making parts of meetings of the Expert Committee.

Applications for inclusion, change or deletion

4. Applications for inclusions, changes or deletions to the Model List may be submitted to the Secretary of the Committee by relevant departments in WHO or by outside individuals or entities including, for example specialist societies, professional groups or pharmaceutical companies. If an application by an outside individual or entity has not been submitted through the relevant department in WHO, the opinion of the relevant department in WHO on any application will be obtained by the Secretary with the application and presented to the Expert Committee. The information that should be submitted with the application is summarized in Box 1. The application should be received at least four months before the meeting of the Expert Committee. Closing dates for each meeting are notified on the web site. For therapeutic categories for which no specific department exists in WHO the application can be submitted through the department of Medicines Policy and Standards. WHO must be free to make all clinical data that are cited in support of an application publicly available on the WHO web site; confidential data will not be accepted.

Box 1. Information to be included with an application for inclusion or deletion of a medicine in the WHO Model List of Essential Medicines

1. Summary statement of the proposal for inclusion, change or deletion
2. Name of the focal point in WHO submitting or supporting the application
3. Name of the organization(s) consulted and/or supporting the application, where relevant
4. International Nonproprietary Name (INN, generic name) of the medicine
5. Dosage form and strength proposed for listing; including adult and paediatric forms if appropriate
6. International availability – sources, if possible manufacturers
7. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)
8. Availability of pharmacopoeial standards (*British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia*)
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)
10. Information supporting the public health relevance
11. Summary of effectiveness in a variety of clinical settings:
 - Identification of clinical evidence of effectiveness and comparative effectiveness (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
 - Summary of available data (appraisal of quality, outcome measures, summary of results)
 - Summary of available estimates of comparative effectiveness
12. Summary of evidence on safety including:
 - Estimate of total patient exposure to date
 - Description of adverse effects/reactions
 - Identification of variation in safety due to health systems and patient factors
 - Summary of comparative safety against comparators
13. Summary of available data on comparative cost¹ and cost-effectiveness within the pharmacological class or therapeutic group:
 - range of costs of the proposed medicine
 - comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)
14. Proposed (new/adapted) text for the *WHO Model Formulary*

¹ The information on cost and cost-effectiveness should preferably refer to average generic world market prices as listed in the *International Drug Price Indicator Guide*, an essential medicines pricing service provided by WHO and maintained by Management Sciences for Health. If this information is not available, other international sources, such as the WHO, UNICEF and Médecins sans Frontières price information service, can be used. All cost analyses should specify the source of the price information.

Review of applications and draft recommendations

5. The step-wise approach for reviewing applications and draft recommendations is summarized in Box 2. A similar process is used periodically to review whole sections of the Model List. In that case the need for review and the selection of the reviewer(s) are considered in close collaboration with the relevant department in WHO.

Box 2. Systematic review of applications

1. The secretary of the Expert Committee checks the application for completeness.
2. The application, with all supporting references, is posted on the WHO web site¹ for review and comments. Comments can be submitted by the general public (individuals and organizations) and these will be posted on the web site.
3. The application is evaluated by members of the Expert Committee and their reviews are posted on the web site. These reviews contains a draft recommendation for the Committee to consider and comments on the draft text for the *Model Formulary*.
4. Comments are provided by relevant WHO departments and are also posted on the web site for a minimum of 30 days.
5. The presenter (member of Expert Committee) reviews the comments and formulates a final text for consideration by the Expert Committee.
6. The Expert Committee reviews the application and all associated comments and provides a recommendation to the Director-General.

¹ <http://www.who.int/medicines/>

Criteria for selection¹

6. The choice of essential medicines depends on several factors, including the disease burden 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.
7. Most essential medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, adherence or in delaying the development of drug resistance in malaria, tuberculosis and HIV/AIDS.

¹ Since the first meeting of the Expert Committee in 1977, criteria for selection of essential medicines have focused on disease prevalence, treatment facilities, safety, efficacy, quality, availability, and cost factors. Descriptions of selection criteria appear in the Ninth Report of the WHO Expert Committee on the Use of Essential Drugs (WHO Technical Report Series, No. 895, 2000), the Eighth Report of the WHO Expert Committee on the Use of Essential Drugs (WHO Technical Report Series, No. 882, 1998), and previous reports of the Committee.

8. 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.
9. 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.

Presentation of recommendations, report of the Expert Committee

10. In its report, the Expert Committee summarizes the reasons for each recommendation with reference to the underlying evidence. The Expert Committee may grade its recommendations depending on the nature of the underlying evidence. When insufficient evidence is available, the Expert Committee specifies that its recommendations are based on expert judgment and experience. The Committee's report also refers to existing standard clinical guidelines. The Expert Committee may specifically indicate in the list medicines for which specialized health care facilities may be needed or which meet all the selection criteria and which are cost-effective within their therapeutic group, but which are not necessarily affordable for all health systems.
11. Presentation of the Model List will be recommended by the Expert Committee based on considerations of clarity and practicality. Previous model lists have been presented in various formats, including one in which medicines considered to be in the main list appear first under each therapeutic group, followed by medicines considered to be in a complementary list.
12. Immediately after the meeting and subject to final approval by the Director-General, the recommended changes to the Model List, the summary of the Expert Committee's report and other relevant information are posted on the WHO web site. The full report of the meeting is published in the WHO Technical Report Series. Translations of the report are published as soon as possible and in close collaboration with WHO regional offices.

WHO Essential Medicines Library

13. In addition to the information on whether a medicine is in the Model List or not, it is important for end-users to have access to information that supports the selection, 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” and is intended to facilitate the work of national committees.

Annex 6

Revised procedure for updating the content of the Interagency Emergency Health Kit

1. The Interagency Emergency Health Kit

1.1 Background

The agencies of the United Nations system and international and nongovernmental organizations are increasingly called upon to respond to large-scale emergencies, many of which pose a serious threat to health. Much of the assistance provided in such situations is in the form of medicines and medical devices (renewable and equipment).

During the 1980s, the World Health Organization (WHO) took up the question of how emergency response could be facilitated through effective emergency preparedness measures. The aim was to encourage the standardization of medicines and medical supplies needed in emergencies to permit a swift and effective response with medicines and medical devices using standard, pre-packed kits that could be kept in readiness to meet priority health needs in emergencies.

1.2 Introduction

The “WHO Emergency Health Kit” was the first such kit when it was launched in 1990. The second kit, “The New Emergency Health Kit 98” was the outcome of a process of revision and further harmonization by WHO in collaboration with many international and nongovernmental agencies. The third version of the kit, the “Interagency Emergency Health Kit 2006” (IEHK 2006), accommodates emergency care of AIDS, the increasing antimicrobial resistance to commonly available antimalarials and antibiotics, injection safety policy, and the experience of agencies using the emergency health kit in the field.

The content of the emergency health kit is based on the health needs of 10 000 people for a period of three months, the acute phase of an emergency. The kit is composed of ten basic units and one supplementary unit.

Over the years, the group of partners involved has grown from two in the early 1980s to more than 10 partners and suppliers in 2006.

1.2.1 **Key principles**

The key principles of the emergency health kit are:

- The kit is developed for a “worst-case scenario” where the health care system is no longer functioning and assumes the highest incidence of cases/morbidity.
- The kit is sent “blindly” to respond immediately to an emergency.
- The cost of the emergency health kit is not a criterion.
- The medicines and medical devices are selected on the basis of “keep it simple and avoid confusion” (e.g. no injectables are available in basic kits, so that they can be used by emergency staff with limited training).
- It is an enabling kit which means that when emergency staff are able to use the medicines and medical devices appropriately, they should do so, otherwise staff should not use them.

1.2.2 **Feedback**

Currently, there is no systematic feedback mechanism in place for the qualitative and quantitative monitoring of the appropriateness of the content of the emergency health kit. However, in the back of the IEHK 2006 booklet, a feedback form has been included to invite users to report on inadequacies in the content of the basic and supplementary kits, and the information provided in the kit booklet. The completed form can be faxed or the feedback can be sent by email to the IEHK Secretariat at WHO.

1.3 **Current revision procedure**

To date the revisions of the content of the emergency health kit were agreed by consensus by the collaborating agencies, but without any clear criteria. When necessary WHO/PSM as the IEHK Secretariat organized meetings with its partners, the IEHK Group: UNICEF, UNFPA, UNHCR, ICRC, IFRC, IOM, Médecins Sans Frontières, PSF, EPN, and Merlin. These ad-hoc meetings did not reach agreement on an official sign-off date in 2003, 2004 and 2005. Suppliers were informed about progress on the revision of the content of the IEHK.

The IEHK Group verifies whether the new content is in line with the recommendations of the WHO Model List of Essential Medicines, WHO standard treatment guidelines, specifications of medical devices defined by UNICEF, and best practices in emergencies. The content is signed off by all partners by them agreeing to the use of the logo of their respective agencies.

1.4 **Need for a streamlined revision procedure**

The revision of the content of the “New Emergency Health Kit 98” started in November 2002 and concluded with the endorsement of the content

of the Interagency Emergency Health Kit 2006 in February 2006. More details are provided in Box 1. One of the recommendations of the IEHK Group meeting held on 31 January 2006 was the need for a shorter, more streamlined and transparent revision procedure.

Box 1. The last update of the emergency health kit: a four-year period

The updating process started in November 2002 with a letter to all partners requesting their commitment to revising the content of the New Emergency Health Kit '98.

A proposed meeting on 16 October 2003 was postponed to 20 April 2004. During this meeting, categories of medicines and devices, including new antimalarials, post-exposure prophylaxis PEP kit and single-use syringes were reviewed. Two other meetings were held on 18 June and 25 August of that year. In July 2005, membership of the IEHK Secretariat changed due to retirement of the responsible WHO staff member. During September and December 2005, the Secretariat continued discussions by email to resolve the last outstanding issues. On 31 January 2006 an IEHK Group meeting was organized to resolve a pending issue. A web version of the IEHK 2006 booklet was posted on 28 April 2006. Printed versions of the booklet in English, French, and Spanish are in preparation.

The variations in emergencies and changing treatment regimens necessitate more frequent reviews of the content of the emergency health kit as a whole to better anticipate needs. Regular small changes to the content of the IEHK will be less problematic for the suppliers who distribute the emergency health kits.

The contents of the IEHK booklet also need to be reviewed to anticipate these regular updates.

1.5 Need for a responsive kit system

Kits developed by individual agencies for specific health conditions, such as cholera, malnutrition, reproductive health, and emergency surgical interventions, may be considered as possible complementary kits to the IEHK. This is part of the move towards a “flexible” emergency kit system.

In addition, the emerging need to develop responses to HIV and AIDS, tuberculosis and chronic conditions, such as diabetes, asthma and cardiovascular diseases can no longer be ignored in emergencies. People on long-term treatment cannot be excluded in the acute phase of emergencies.

The inclusion of formulations for children for priority diseases also needs to be considered.

The emergency health kit is a means of responding swiftly to the acute phase (first three months) of an emergency, but it is known that these kits are inappropriately used months and even years after the emergency started. As indicated in the information section of the IEHK 2006 booklet, the kit is **not** recommended for re-supplying existing health care facilities. Requirements

for further supplies should be assessed and medicines and medical devices ordered through the national supply system as soon as possible.

To respond to supply gaps for HIV, AIDS, tuberculosis, chronic conditions and emergency surgical interventions in disasters, it has been suggested that quantified lists should be developed, rather than kits to respond to acute needs.

2. Streamlined revision procedure to update the content of the IEHK

A similar procedure to the one for updating the Model List of Essential Medicines is envisaged, which will allow for wider consultation, and an evidence-based and therefore more efficient process.

2.1 Guiding principles for the new revision procedure

A new procedure for updating the IEHK will be based on major features of the revision procedure of the WHO Model List of Essential Medicines,¹ such as:

1. The *updated WHO Model List of Essential Medicines* and WHO standard treatment guidelines will be the baseline references for considering a proposed revision of the content of the IEHK. The term “essential medicines” will be used instead of “essential drugs”, reflecting the common use of the term “medicines” to describe pharmaceutical preparations in clinical health care practice. Product availability is one of the criteria for inclusion of a medicine on the Model List and any comment on availability made by the Expert Committee will be taken into account.
2. A *systematic approach* will be adopted to manage proposals for the deletion, change to or inclusion of medicines and medical devices in the current IEHK.
3. A *transparent process* will be adopted for selecting and estimating medicines and medical devices to be included in the kit, including systematic analysis of effects and appropriateness of medicines and medical devices proposed for use in emergency care for different health conditions.
4. *Full involvement* of different WHO departments and other partner UN agencies and international organizations operating in emergencies will be pursued, especially during the application and review process, linking the process to clinical guidelines and essential emergency equipment

¹ WHO medicines strategy. Revised procedure for updating WHO's Model List of Essential Drugs. Report by the Secretariat. EB/109/8; 7 December 2001.

lists disseminated by WHO, medical devices specifications from UNICEF, and best practices in emergencies pursued by all departments and partners.

5. *Opportunities to react for interested parties*, including WHO's regional and country offices, relevant UN agencies, international organizations and nongovernmental organizations, will be offered with regard to both applications and draft recommendations prior to the meeting of the IEHK Review Committee. Applications and draft recommendations will be available on the WHO web site.
6. *The IEHK Review Committee* is composed of representatives of UN agencies, and international organizations and nongovernmental organizations operating in emergencies, who endorse the IEHK. Relevant WHO staff members will be invited to attend the IEHK Review Committee meeting as technical advisers.
7. *The Secretariat of the IEHK Review Committee* is the WHO Department of Medicines Policy and Standards (PSM).
8. *Membership of the IEHK Review Committee* is open to organizations which endorse the content of the IEHK and participate actively in the process of revision of the kit.
9. The list of items in the IEHK is a *core list* to which all agencies should adhere.
10. The *absolute cost of the treatment* will not constitute a reason to exclude a medicine and/or a device from the IEHK that otherwise meets the stated selection criteria.
11. The *patent status* of a medicine is not considered in selecting medicines for the IEHK.

2.2 **Terms of reference of the IEHK Secretariat and Review Committee**

2.2.1 **Terms of reference**

The IEHK Secretariat

The IEHK Secretariat is the WHO Department of Medicines Policy and Standards (PSM). It is responsible for instigating reviews of the content of the IEHK, developing and maintaining a specific web site, organizing meetings of the IEHK Review Committee, and collecting and sharing relevant information with IEHK partners and suppliers. The Secretariat will be responsible for the publication of the updated IEHK booklet in print and electronic versions.

The IEHK Review Committee

The IEHK Review Committee is composed of representatives of UN agencies, and representatives of technical organizations and nongovernmental organizations operating in emergencies, who endorse the IEHK. Relevant WHO staff members will be invited to attend the IEHK Review Committee meeting as technical advisers. The Committee is responsible for the regular updates of the content of the IEHK. It will guarantee adherence to the guiding principles and procedure for revision of the IEHK.

Individual Committee members will be involved in the review of applications and will draft recommendations. They will propose text for basic treatment protocols. Technical advisers may assist in the review process and contribute to consolidated recommendations.

2.2.2 Commitment

WHO/PSM is committed to being the Secretariat of the IEHK Review Committee. IEHK Review Committee members will represent their organization in the IEHK Review Committee for at least two years to guarantee continuity.

2.2.3 Funding

The Secretariat will guarantee sufficient funding for its tasks, including the publication of the IEHK booklet.

The individual members of the IEHK Review Committee will fund themselves for attendance at meetings and can allocate official time to review applications when requested.

2.3 Decision-making process by consensus

At the scheduled meeting of the IEHK Review Committee all prepared recommendations of the received applications, and relevant comments posted on the web will be reviewed. Discussion will focus on comparing efficacy, safety and suitability of products, and on reviewing the structure of the kit.

Final decisions will be made on the basis of consensus. In the case that consensus cannot be reached on a particular issue, it will be put on the agenda of the next Committee meeting and the item in the kit will not be changed.

2.4 Submission of applications for inclusion, change or deletion

Applications for inclusions, changes or deletions to the content of the IEHK are submitted by departments of WHO, other UN agencies, international organizations and nongovernmental organizations operating in emergencies, to the Secretariat of the IEHK Review Committee. The information that should be submitted with the application is summarized in Appendix 1.

The procedures for submitting and reviewing applications, for drafting recommendations and for the decision-making process for accepting or refusing recommendations are summarized in Appendix 2.

A similar process is used periodically to review the contents of the IEHK booklet. In that case the need for review and the selection of the reviewer(s) are considered in close collaboration with the IEHK Secretariat.

2.5 Principles for selection of essential medicines and medical devices

The choice of essential medicines and medical devices in emergencies depends on several sources of information, including:

- epidemiological data;
- population profiles;
- disease patterns; and
- assumptions based on experience gained by UN agencies and international organizations in emergency situations.

Factors that influence the selection of medicines and devices are:

- The most peripheral level of health care may be staffed by health care workers with limited medical training, who treat symptoms rather than diagnosed diseases using the basic units, and refer patients who need more specialized treatment to the next level of care.
- The proportion of patients presenting themselves with the more common symptoms or diseases can be predicted.
- The first referral level of health care is staffed by general doctors, experienced nurses, midwives or medical assistants, with no or limited facilities for inpatient care. They will use the supplementary unit in conjunction with one or more basic units.

The criteria for the selection of essential medicines and medical devices are as follows:

- Sound and adequate data should be available on the efficacy, safety and suitability of selected treatment regimens in the context of emergencies. WHO standard treatment guidelines and the WHO Model List of Essential Medicines are the references for the selection of medicines included in the kit.
- Stability in various conditions, the need for special diagnostic or treatment facilities and pharmacokinetic properties are also considered, if appropriate.
- Most selected medicines should be formulated as single compounds. Fixed-dose combination products are selected only when the combination has a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately.

2.6 Estimation of quantities of medicines and medical devices

- Estimation of quantities of a medicine and a medical device in the kit is based on:
 - average morbidity patterns among displaced populations;
 - use of standard treatment guidelines;
 - figures and data provided by agencies with field experience.
- During emergencies, the estimate of the average number of visits for advice or treatment to such facilities by every individual is four times per year.
- Half of the population who will need assistance is under 15 years of age.
- The estimated rate of referral from the most peripheral to the next level of health care is 10%.
- Based on attendance estimates, the supplies included in one IEHK (10 basic units and 1 supplementary unit) serve the needs of a population of 10 000 people for a period of approximately 3 months.
- Each of the 10 **basic units** contains medicines, medical devices (renewable and equipment), for 1000 people for 3 months. The **supplementary unit** contains medicines, medical devices (renewable and equipment) to be used at the first referral level for 10 000 people for 3 months. To be operational, the supplementary unit should be used together with at least one basic unit.
- Estimation of need for medical devices will be complementary to estimation of need for medicines: e.g. estimation of the need for syringes is based on the number of injectable medicines included in the supplementary unit, which are to be used in accordance with the treatment guidelines provided.

2.7 Presentation of recommendations

In its meeting report, the IEHK Review Committee will summarize the reasons for each recommendation and make the reasons for its decisions explicit.

Immediately after the IEHK review meeting, the approved changes to the content of the kit and the meeting report will be posted on the WHO web site.

Appendix 1

Information to be included with an application for inclusion or change of a medicine or medical device in the IEHK

The following information should be included with an application for inclusion or change of a medicine or medical device in the IEHK:

1. Summary statement of the proposal for inclusion or change, in the context of an emergency situation.
2. Name of the responsible person and organization submitting the application.
3. Name of the organization(s) consulted and/or supporting the application.
4. Consequences for other items present in the kit (e.g. number of syringes for injectables);
5. Information requested for medicines:
 - International Nonproprietary Name (INN, generic name) of the medicine;
 - additional information on suitability for use in emergencies besides clinical information provided by the WHO Expert Committee on the Selection and Use of Essential Medicines;
 - information supporting the health emergency or public health relevance, including epidemiological information on disease burden and assessment of current use;
 - treatment details, including dosage regimen, duration; reference to existing WHO and other clinical guidelines; or treatment facilities;
 - quantities proposed, including information about the method used, if this is an application for a change or inclusion;
 - availability of suppliers, with summary of regulatory status of and quality information on the medicine.
6. Information requested for devices:
 - device name and short description from UNICEF or other suitable source;
 - for newly proposed devices, provide device name and full specifications;
 - information supporting the health emergency or public health relevance, including epidemiological information on disease burden and assessment of current use;
 - description of current use, including need for medical devices, special diagnostic or treatment facilities;
 - quantities proposed if this is an application for a change or inclusion;
 - consequences for other items present in the kit (e.g. number of syringes for injectables);
 - availability of supplier(s), with quality information.

Appendix 2

Information to be included with an application for deletion of a medicine or medical device from the IEHK

The following information should be included with an application for deletion of a medicine or medical device from the IEHK:

- summary statement of the proposal for deletion;
- name of the responsible person and organization submitting the application;
- name of the organization(s) consulted and/or supporting the application;
- consequences for other items present in the kit;
- information requested for medicines:
 - International Nonproprietary Name (INN, generic name) of the medicine;
 - information supporting the request for deletion;
- information requested for devices:
 - device name and short description from UNICEF, or other appropriate source;
 - information supporting the request for deletion.

Appendix 3

Procedures for the review of applications and for the development of recommendations

- The deadline for submitting an application will be five months prior to the meeting of the IEHK review committee for updating the content of the IEHK.
- The IEHK Secretariat will check submitted applications for completeness and verify with the relevant WHO department whether the proposed product is consistent with current standard treatment guidelines.
- Verified applications will be posted on the WHO web site for review and comments at least three months prior to the meeting; the closing date for comments will be one month prior to the meeting.
- Each verified application will be reviewed and recommendations drafted by two members of the IEHK review committee who will attend the meeting.
- The review(s), draft recommendation(s) and proposed text for the basic treatment protocol for inclusion in the IEHK booklet will be prepared by the relevant WHO departments and members of IEHK review committee. They will also be posted on the WHO web site for comments, for a minimum of 30 days.
- At the scheduled IEHK meeting, the IEHK review committee will discuss the application(s) and drafted recommendation(s) and proposed text for the basic treatment protocol, if appropriate and will finalize the recommendations for the IEHK.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The international pharmacopoeia, fourth edition.

Volume 1: general notices; monographs for pharmaceutical substances (A–O)

Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.

2006 (1500 pages), also available in CD-ROM format

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms

1998 (94 pages)

Basic tests for pharmaceutical dosage forms

1991 (134 pages)

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials.

Volume 1: 1997 (244 pages)

Volume 2: Good manufacturing practices and inspection.

2nd updated edition, 2007 (in press)

Quality control methods for medicinal plant materials

1998 (123 pages)

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Forty-first report.

WHO Technical Report Series, No. 943, 2007 (156 pages)

International nonproprietary names (INN) for pharmaceutical substances. Cumulative list no. 11.

2004 (available in CD-ROM format only)

WHO Expert Committee on Biological Standardization

Fifty-fifth report.

WHO Technical Report Series, No. 932, 2006 (146 pages)

WHO model formulary

2006 (available in CD-ROM format only)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization, 1211 Geneva 27, Switzerland
(tel. +41 22 791 3264; fax: +41 22 791 4857;
e-mail: bookorders@who.int; order on line: <http://www.who.int/bookorders>)

This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model List of Essential Medicines. The first part contains a summary of the Committee's considerations and justifications for additions and changes to the Model List, including its recommendations. Annexes to the main report include the revised version of the WHO Model List of Essential Medicines (the 15th) and a list of all items on the Model List sorted according to their 5-level Anatomical Therapeutic Chemical (ATC) classification codes. Other annexes cover the proposed procedure for updating and disseminating the WHO Model List of Essential Medicines, and the revised procedure for updating the content of the Interagency Emergency Health Kit.

ISBN 9789241209465



9 789241 209465
