Contents

PART ONE 17th Expert Committee on the Selection and Use of Essential Medicines......... 9

1. Introduction ...................................................................................................................................... 16
2. Open session...................................................................................................................................... 16
3. Proposal for revision of listing pharmaceutical products.............................................................. 19
4. Review of other matters.................................................................................................................... 20
5. Review of missing essential medicines for HIV ................................................................................ 20
7. New applications for paediatric medicines....................................................................................... 26
   Section 6: Anti-infective medicines .................................................................................................. 26
   Section 6.2: Antibacterials .................................................................................................................. 26
   Procaine benzylpenicillin (Review) -- (EMLc)................................................................................. 26
   Section 6.2.4: Antituberculosis medicines (Review, EMLc) ............................................................... 27
   Section 6.3: Antifungal medicines ..................................................................................................... 29
   Liposomal amphotericin B (Inclusion in the EMLc).......................................................................... 29
   Section 6.5: Antiprotozoal medicines ............................................................................................... 30
   Section 6.5.3: Antimalarial medicines ............................................................................................. 30
   Artemether + lumefantrine (Inclusion in the EMLc)........................................................................... 30
   Section 7: Antimigraine medicines .................................................................................................... 30
   Ibuprofen (Inclusion in the EMLc)..................................................................................................... 30
   Section 12: Cardiovascular medicines ............................................................................................. 31
   Section 12.4: Medicines used in heart failure ................................................................................... 31
   Captopril (Inclusion in the EMLc)...................................................................................................... 31
   Carvedilol (Inclusion in the EMLc).................................................................................................... 31
   Section 17: Gastrointestinal medicines ............................................................................................ 32
   Section 17.2: Antiemetic medicines (Inclusion of odansetron in the EMLc)........................................ 32
   Section 18: Hormones....................................................................................................................... 32
   Section 18.5: Insulins and other antidiabetic agents........................................................................ 32
   Access to Essential Diabetes Medicines for Children in the Developing World.............................. 32
9. ................................................................................................................ Applications for the 16th Model list ........................................................................................................................... 34
Section 4: Antidotes and other substances used in poisonings.......................................................................................... 34
Section 4.2: Specific ........................................................................................................ 34
Pralidoxime (Inclusion) ........................................................................................................ 34
Section 5: Anticonvulsants/antiepileptics ........................................................................... 34
Lamotrigine (Inclusion) ........................................................................................................ 34
Addition of lorazepam and midazolam ................................................................................ 35
Lorazepam (Inclusion) ........................................................................................................ 36
Midazolam (Inclusion) ........................................................................................................ 36
Section 6: Anti-infective medicines .................................................................................. 37
Section 6.2: Antibacterials ............................................................................................... 37
Section 6.2.4: Antituberculosis medicines ..................................................................... 37
Rifabutin (Inclusion) ........................................................................................................ 37
Section 6.4: Antiviral medicines ...................................................................................... 38
Section 6.4.2: Antiretrovirals .......................................................................................... 38
Atazanavir (Inclusion) ........................................................................................................ 38
Protease inhibitors (Review) ............................................................................................ 39
Fixed-dose combinations .................................................................................................. 41
Zidovudine + lamivudine + abacavir (Inclusion) (AZT/3TC/ABC) .................................. 41
Section 6.4.3: Other antivirals ......................................................................................... 42
Amantadine and rimantadine, oseltamivir, zanamivir (Inclusion) .................................. 42
Section 6.5: Antiprotozoal medicines .............................................................................. 43
Section 6.5.5: Antitrypanosomal medicines ................................................................ 43
Nifurtimox + eflornithine (Inclusion) ................................................................................ 43
Section 7: Antimigraine medicines .................................................................................. 44
Sumatriptan (Inclusion) .................................................................................................... 44
Section 8: Antineoplastic, immunosuppressives and medicines used in palliative care ...... 45
Section 8.2: Cytotoxic medicines .................................................................................... 45
Carboplatin (Inclusion) .................................................................................................... 45
Hydroxycarbamide (Inclusion) ....................................................................................... 45
Ifosfamide (Inclusion) ..................................................................................................... 46
Mesna (Inclusion) ........................................................................................................... 47
Section 10: Medicines affecting the blood ....................................................................... 47
Tranexamic acid (Inclusion) ............................................................................................. 47
Section 12: Cardiovascular medicines ............................................................................. 48
Section 12.2: Antiarrhythmic medicines ........................................................................ 48
Amiodarone (Inclusion) .................................................................................................. 48
Section 12.4: Medicines used in Heart Failure ................................................................ 49
Hydrochlorothiazide (New formulations) ....................................................................... 49
Quinidine (Deletion) ...................................................................................................... 49
Section 17: Gastrointestinal medicines ................................................................. 50
Section 17.1: Antiacids and other antiulcer medicines ........................................ 50
Omeprazole (Inclusion) .......................................................................................... 50
Section 17.5: Medicines used in diarrhoea ............................................................ 51
Endar (Inclusion) ................................................................................................. 51
Oral rehydration salts (Inclusion) ........................................................................ 51
Section 22: Oxytocics and antioxytocics ............................................................... 52
Misoprostol (Inclusion) ......................................................................................... 52
Section 24: Psychotherapeutic medicines ............................................................ 53
Section 24.1: Medicines used in psychotic disorders ........................................... 53
Clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone (inclusion) .................................................................................................................. 53
Section 24.2: Medicines used in mood disorders .................................................. 54
Section 24.2.1: Medicines used in depressive disorders .................................... 54
Fluoxetine, paroxetine and sertraline (Inclusion) .................................................. 54
Section 24.3: Medicines used in generalized anxiety and sleep disorders ......... 55
Addition of a selective-serotonin reuptake inhibitor (escitalopram, paroxetine and sertraline) ................................................................................................................................................ 55
Section 24.5: Medicines used in substance dependence programmes ............... 56
Nicotine Replacement Therapy (NRT) (Inclusion) ............................................. 56
Section 25: Medicines acting on the respiratory tract ......................................... 56
Section 25.1: Antiasthmatic and medicines for chronic obstructive pulmonary disease ........................................................................................................ 56
Beclometasone (New formulation) ..................................................................... 56
Cromoglicic acid (Re-instatement) .................................................................... 57
Summary of recommendations ............................................................................ 58
Additions, changes and deletions to the Model List ........................................... 58
Additions, changes and deletions to the EMLc ................................................. 61
Appendix 1: Proposed lists of priority essential medicines for HIV ................. 63
Appendix 2: Report of the Informal Expert Meeting on Dosage Forms of
Medicines for Children ....................................................................................... 67
ANNEX 1: 16th Essential Medicines List ............................................................... 79
ANNEX 2: Second EMLc ........................................................................................ 81
ANNEX 3: The Anatomical Therapeutic Chemical (ATC) classification system .. 83
ANNEX 4: Alphabetical list of essential medicines
(with ATC classification code numbers) ................................................................ 85
PART TWO Second Meeting of the Subcommittee of the Expert Committee on the
Selection and Use of Essential Medicines .......................................................... 87
1. Introduction ...................................................................................................... 91
2. Open session .................................................................................................... 91
3. Review of terms of reference ......................................................................... 92
4. The WHO Model List of Essential Medicines for Children – by section

Section 4. Antidotes and other substances used in poisonings

Section 4.1 Non-specific
Charcoal, activated (review)

Section 4.2 Specific
Acetylcysteine (review)
Pralidoxime (inclusion)

Section 6. Anti-infective medicines

Section 6.2 Antibacterials

Section 6.2.1 Beta-lactam medicines
Cefalexin (inclusion)
Procaine benzylpenicillin (review)
Ceftazidime (review)
Ceftriaxone
Carbapenems (review)

Section 6.2.2 Other antibacterials
Fluoroquinolones (review)
Tetracycline (review)
Gentamicin (review)
Sulfadiazine (review)

Section 6.2.4 Antituberculosis medicines (review)

Section 6.4.2 Antiretrovirals (new formulations)

Section 6.5: Antiprotozoal medicines

Section 6.5.2: Antileishmaniasis medicines
Liposomal amphotericin B (inclusion)

Section 8: Antineoplastic, immunosuppressives and medicines used in palliative care

Section 8.2: Cytotoxic medicines (review)

Section 8.4: Medicines used in palliative care (inclusion)

Section 12: Cardiovascular medicines
Quinidine (review)
Rheumatic fever and rheumatic heart disease (review)

Section 13: Dermatological medicines (topical)
Dermatological medicines (review)

Section 15: Disinfectants and antiseptics
Chlorhexidine (new formulation)

Section 17: Gastrointestinal medicines
Pancreatic enzymes (inclusion)

Section 17.2: Antiemetic medicines (review)

Section 18: Hormones, other endocrine medicines and contraceptives
Hydrocortisone and fludrocortisone (inclusion)
Section 24: Psychotherapeutic medicines (review) ................................................................. 126
Section 25: Medicines acting on the respiratory tract ........................................................ 127
  Salbutamol (review) ........................................................................................................ 127
Section 27: Vitamins and minerals ....................................................................................... 128
  Retinol .............................................................................................................................. 128
New Section 28: Ear, nose and throat conditions in children .......................................... 129
New Section 29: Essential medicines for neonates ......................................................... 130
5. Summary of recommendations .................................................................................... 132
References of the Second Report of the Subcommittee .................................................. 136
Appendix A: Declaration of interests of Subcommittee members .................................. 141
Appendix B: Essential medicines that can be used in neonates .................................... 143
References ........................................................................................................................ 147
PART ONE

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Declaration of interests of Members of the 17th Expert Committee on the Selection and Use of Essential Medicines

The Members reported the following:

Dr Noël Cranswick reported being an investigator on clinical trials for GlaxoSmithKline, Wyeth, Pfizer, Eli Lilley and UBC (but not for any products or products being considered at the meeting or related to them) and also reported being involved in a clinical trial for Biota.

Dr Alexander Nii Oto Dodoo reported receiving a research support grant from WHO to study the PV of LAPDAP and amodiaquine-artesunate. Grant no. A40471.

Dr Andy Gray reported having accepted travel support from AstraZeneca, Fresenius Kabi and Aspen Pharmacare to attend continuing education events as a guest speaker, and also receiving research support grants from various donors of antiretroviral medicines used in ACTG and IMPAACT trials and from Gilead Sciences. He also reported being a member of the Scheduling and Naming Expert Committee of the South African Medicines Control Council and being a director of a government funding agency for biotechnology.

Dr Kalle Hoppu reported giving one time consultation advice on behalf of the Finnish Investigators Network for Pediatric Medicines to Lundbeck A/S, Denmark and also a written clinical expert opinion for a regulatory submission to Oy Leiras, Finland Ab.

Dr Marcus M. Reidenberg reported being a member of a data safety and monitoring board for Roche; receiving royalties through the National Institutes of Health (NIH) on the use of gossypol for cancer; and being a consultant to and holding stock in Ascenta, a privately-held clinical stage biopharmaceutical company, which does not have any have products on the market at this time — consultant for The Medicines Company.

Dr Anita Zaidi reported receiving research funding from Wyeth in the area of pneumococcal surveillance.

Mrs Jehan Mohammed Ali Al-Fannah, Dr Lisa A. Bero, Professor Abdol Majid Cheraghali, Dr Rohini Fernandopulle, Dr Myriam Henkens, Dr Gregory Kearns Mr Edgard José Narvàez Delgado, Dr Lenita Wannmacher, reported no conflict of interest.

The Temporary Advisers reported the following:

Professor Cleotilde Hidalgo How reported acting as a consultant on a National TB program Task Force involved in the revision of a training manual.

Dr Gitanjali Batmanabane, Professor Dai Yao Hua, Dr Elizabeta Zisovska reported no conflict of interests.
Contracts were awarded to the following WHO Collaborating Centres, organizations and individuals for work undertaken in preparation for the Expert Committee Meeting on the Selection of Essential Medicines:

WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health, NHS Centre for the Evaluation of Effectiveness of Healthcare, Modena, Italy — Applications for amiodarone, hydrochlorothiazide and lamotrigine.

WHO Collaborating Centre for Pharmaco-economics and Rational Pharmacotherapy, University of Newcastle, New South Wales, Australia — Application for antivirals, antiemetic medicines, cytotoxics (carboplatin, hydroxycarbamide, ifosfamide, mesna) procaine benzylpenicillin, tranexamic acid.

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Verona, Italy — Application for escitalopram, paroxetine and sertraline.


Dr Sean Beggs, General Paediatrician and Paediatric Clinical Pharmacologist, Royal Hobart Hospital, Senior Lecturer, University of Tasmania — Applications for captopril and carvedilol.

Professor Emilio Perucca, Head, Clinical Trial Center, Institute of Neurology IRCCS C Mondino Foundation and Professor of Medical Pharmacology, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy — Application for lorazepam and midazolam.

Dr Patti Whyte, Griffith University, Queensland, Australia — Applications for atazanavir, zidovudine + lamivudine + abacavir and liposomal amphotericin B.
1. Introduction

The 17th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 23rd to 27th March 2009. The meeting was opened on behalf of the Director-General by Dr Hans V. Høgerzeil, Director of the Department of Essential Medicines and Pharmaceutical Policies (EMP). He stated that the WHO’s medicine programme and the recommendations of its Expert Committee played an important role in the context of supporting access to primary care and championing the use of evidence based medicine, which have been identified by the Director-General as priority areas for WHO. He noted that this would be the fifth meeting of the Expert Committee operating under the 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 transparency of the process. Dr Høgerzeil also briefly explained some aspects of the Committee procedures. He stated that the Committee is not a representative one; all member participate in their own personal capacity and are not allowed to take instructions from any government or any other authority.

2. Open session

The open session of the meeting was opened by Dr Hans V. Høgerzeil. He discussed the purpose of the open session and it was highlighted that this was an opportunity for all stakeholders to participate in the discussions and to comment on issues relating to the WHO Model List of Essential Medicines. It was also noted that the open session provides an opportunity for members of the Expert Committee to receive first-hand, additional information and opinions on matters under consideration that would be noted and taken into consideration by the Committee when formulating final recommendations in subsequent private sessions.

Discussions and opinions put forward during the open session are reflected in the report of the meeting. 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 the report but remain available on the WHO web site (http://www.who.int/selection_medicines/committees/expert/17/en/index.html).

As part of the open session, participants were briefed about various activities relating to the Model List. This included an update on activities in regions to disseminate and implement the WHO Model List of medicines, including workshops in the South East Asian, Western Pacific and European regions. Points highlighted included the need for national processes of selection to be updated especially with regards to committee membership and potential conflicts of interest; the importance of developing linkages between treatment guidelines and national EMLs and procurement and the potential value of sub-regional harmonization of selection processes.

Participants were also provided with a brief update on activities in relation to WHA resolution 60.20, Better Medicines for Children. Activities highlighted were the pre-ICDRA meeting (September 2008) on regulatory strategies for improving medicines for children, the work on defining optimal dosage forms of medicines for children that was on the agenda for
the Expert Committee and the need to develop strategies that would be effective in improving use of medicines in children in many different countries and settings.

A number of organizations made statements that were discussed during the open session.

**UNITAID**

The UNITAID Secretariat advised the Committee of its work towards a patent pool for medicines. Initially, the focus is to be on priority medicines for HIV, concentrating on those products that are needed but are not yet developed, such as second-line medicines and paediatric formulations; and on those existing products for which the number of suppliers is insufficient to create economies of scale. Once up and running, the pool could expand to serve other disease areas of need. The UNITAID Secretariat and WHO proposal requested advice from the Committee on what might be priority ‘missing essential’ medicines for consideration for inclusion in a patent pool.

**Tobacco Free Initiative**

A representative from the Tobacco Free Initiative, WHO, outlined the potential benefits of nicotine replacement therapy (NRT) for aiding smoking cessation, as presented in the application for inclusion of this medicine on the WHO Model List of Essential Medicines. It was highlighted that a third of the world’s population smoke and that if current patterns do not change, up to 1 billion people could die from smoking tobacco this century. Nicotine replacement therapy is one of the possible ways to support smoking cessation. The Committee were informed that many people, particularly in low-income countries face substantial barriers to obtaining NRT, which could be removed if NRT was an essential medicine.

**International Union Against Cancer (UICC)**

A representative from UICC spoke in support of the application to include NRT on the WHO Model List of Essential medicines, highlighting that each year, tobacco-related diseases claim nearly 6 million lives and that this will increase to 10 million per year in a few decades. It was suggested that a major advancement in combating the harmful effects of tobacco has come from the realization that tobacco addiction is not merely a personal bad habit, but a medical problem that can be addressed via medical interventions. It was stated that the likelihood of successful smoking cessation approximately doubles when nicotine replacement therapies are employed. The UICC strongly endorsed the addition of nicotine replacement therapies to the WHO Model List of Essential Medicines.

**World Self-Medication Industry (WSMI)**

A representative from the WSMI also spoke in support of the inclusion of NRT on the WHO Model List of Essential Medicines. The Committee were informed that WSMI is a federation of over 50 member associations representing manufacturers and distributors of non-prescription medicines on all continents. It was reported that based on evidence, NRT has in many countries been switched from prescription to non-prescription status and made available in a variety of presentation forms: chewing gum, patches, inhalers, lozenges and tablets. They stated that inclusion of NRT on the Model List would help to encourage countries, which at the present time do not have NRT as widely available as needed by
smokers, to make NRT more widely available through all possible channels and in a variety of forms.

**Médecins Sans Frontières (MSF)**

The Committee was informed about the Médecins Sans Frontières Campaign for Access to Essential Medicines. Médecins Sans Frontières discussed the importance of the EML as a tool to help rationalize the use of essential medicines. However, it was pointed out to the Committee that its presentation is currently cumbersome with the inclusion of many footnotes and a confusing mixture of medicines information in terms of dosage forms with treatment guidance. It was recommended that a clear distinction be made between the EML and treatment guidelines or therapeutic protocols and that a supplementary column should be added to the right hand side of the list for the inclusion of all footnotes regarding restricted use and protocols.

MSF indicated its support for:

- the inclusion of nifurtimox, for use in combination with eflornithine for the treatment of stage 2 Human African Trypanosomiasis;
- the inclusion of a dispersible formulation of artemether + lumefantrine because of its easier administration in children;
- the inclusion of misoprostol tablets for the management of the third stage of labour, post-partum haemorrhage and for completing an incomplete abortion as a useful alternative to oxytocin injection.

MSF welcomed the combined UNITAID and WHO initiative for the development of a patent pool to improve the availability of priority essential medicines for HIV.

**Drugs for Neglected Diseases (DNDi)**

A representative of DNDi made a statement in about the proposal for inclusion of nifurtimox + eflornithine combination therapy to the Model List. The Committee were informed that stage 2 *Trypanosoma brucei gambiense* Human African Trypanosomiasis is a fatal disease which threatens millions in sub-Saharan Africa. Given that (1) 70% of patients are still receiving melarsoprol that is toxic and increasingly ineffective; (2) difficulties with use of eflornithine as monotherapy; (3) the potential for developing to resistance to eflornithine when used in monotherapy, the addition of nifurtimox would significantly reduce the number of injections of eflornithine required and decrease the cost of the treatment of HAT. It was also highlighted that clinical trials in this area are very complicated and that the next possible new treatment for this disease will not be available for at least 6-7 years.

**UNICEF statement**

A representative from UNICEF addressed the Committee regarding the importance of the Essential Medicine List and medicines selection in supply chain management. The Committee were told that UNICEF takes guidance from the list and is particularly pleased that in recent years there has been a focus on medicines for children. The Committee were informed that UNICEF plays a "market shaping" role for a few strategic products that are
listed on the EML and requested by programmes. This role includes aggregating needs and influencing industry to improve availability, pricing, quality and innovation of essential products. The representative stated that UNICEF is committed to working with WHO and manufacturers for the development of relevant new products, including medicines for children. They welcomed the initiative of UNITAID for the development of a patent pool for priority medicines.

3. Proposal for revision of listing pharmaceutical products

The Committee reviewed the proposals by the Medicines Quality Assurance Programme, Quality and Safety: Medicines (QSM) regarding the listing of pharmaceutical products in the EMLs. The Committee noted that many inconsistencies have arisen over time in relation to pharmaceutical products currently available across the world and that these inconsistencies often reflect local or regional differences or long established practices. It agreed that it was necessary to clarify the Committee’s policy for specifying dosage forms and strengths on the list.

The Committee agreed on three actions.

Firstly, the Committee agreed that the principle of choice of dosage forms is that where several forms are possible the most general form would be used. It accepted the proposal from QSM that the section ‘Explanatory Notes’ in the EML should be expanded to provide more information and guidance to users in regards to dosage form terminology and medicine strength. Where there is a clinical advantage for use of a specific form, for example, dispersible tablet, the form would be specified. The Explanatory Notes should also to include a link to the information about assuring quality of medicines on the WHO EMP/QSM website.

Second, for future listings the Committee agreed on the following principles.

1. The medicines listed in the left-hand column of the EML will be named as the active moieties, using the International Nonproprietary Name (INN), wherever applicable.
2. Entries in the right-hand column of the EML will provide information on the dosage forms and on the strengths (for example, the weight per tablet) of products, as found to be available in the WHO Member States.

In manufacturing a dosage form, the active pharmaceutical ingredient (API), may be the active moiety per se or it may consist of the active moiety together with one or more additional chemical groups/ radicals, depending on the nature of the molecule. Commonly APIs are salts, esters or hydrates of the active moiety and are named using an appropriate Modified INN (INNM). In cases where the API is not the active moiety, the entry in the right-hand column in the EML will indicate the form of the API used in the dosage form by specifying the name of the salt, ester etc.

The way that the strengths of dosage forms are expressed in entries in the right-hand column (RHC) of the EML reflects the way that the strength of products are available (and labeled)
on the market in WHO Member States. Where the strength of products available is expressed in terms of the active moiety, the name of the salt, ester etc is specified in brackets and preceded by the word "as". An amount given in the right-hand column of the EML is then to be interpreted as an amount of the active moiety listed in the left-hand column (LHC).

**Example: the listing for ampicillin would be,**

LHC: Ampicillin  
RHC: powder for injection 500 mg and 1 g (as sodium salt)  
*This is to be interpreted as 500 mg and 1g of ampicillin.*

Where the strength of products available is expressed in terms of the API, the full name of the API including the salt, ester etc is specified in the right-hand column of the EML.

**Example: the listing for codeine would be,**

LHC: codeine  
RHC: tablet: 30 mg codeine phosphate  
*This is to be interpreted as 30 mg of codeine phosphate.*

For a small number of medicines, in particular certain long-established medicines for which different salts are used as APIs, there are significant differences in the way that products available in WHO Member States are labelled with respect to strength. Where necessary, in these and other instances of potential confusion, a warning note will be included. In such cases further guidance may be found in the WHO Model Formulary.

Third, the Committee requested the Secretariat to review current entries on the list and revise them according to the above principles. This list will be provided at the next meeting.

Finally, the Committee reviewed a lists of medicines that are currently listed in a range of strengths (e.g. paracetamol 100 mg to 500 mg) and recommended that they be retained as currently listed to accommodate the wide range of strengths currently available.

### 4. Review of other matters

The Expert Committee discussed how to enhance the use of the WHO Model List of Essential Medicines to improve rational use of medicines. The Committee noted the interventions listed in the WHO medicines strategy 2008-2013 and the World Health Assembly Resolution 60.16. When enhancing the use of the EML, WHO should make people aware that the EML is a part of a globally applicable concept designed to ensure the widest possible access to effective medicines of assure quality. The concept includes the process of selection of medicines using standard principles of evidence-based medicine, that is, a formal assessment of comparative effectiveness, safety and cost. While one product of this process is the WHO Model List of Essential Medicines, the same process can be used for selection of lists of medicines for other purposes, such as national reimbursement schemes.
The Committee suggested the following approaches as ways of enhancing the EML process and ‘product’:

- WHO should work to increase awareness of the EML among policy makers, health care workers.
- Information about the EML selection process and products should be included in the curriculum of healthcare students (e.g. doctors/pharmacists/nurses).
- WHO should adhere to an evidence based approach to change practice and ensure that the evidence base is available to member states. For example, WHO could work with the Effective Practice and Organization of Care Group in the Cochrane Collaboration to disseminate information on effective interventions to improve prescribing and use of medicines.
- The WHO should increase advocacy to health care providers through engagement with professional organizations as opinion leaders, noting that there are many experts within the regions who are willing to help locally.
- The WHO should explore mechanisms for making the evidence used to make selection decisions for the EML available to the Member States.
- The WHO should enhance the implementation strategies for the WHO Model Formulary.

The Committee noted the work of the WHO-UN program on Pre-qualification of medicines. The Committee agreed in principle that WHO should pre-qualify manufacturers of medications in the EML to guarantee quality. The WHO should explore possibilities of expanding the scope of the program, taking into account priority diseases, availability and manufacturer of API, and a need to support the national regulatory authorities and mechanisms for ensuring quality of API and final dosage forms.

The Committee discussed how the Advisory Committee on Safety of Medicines could enhance or improve on the current activities of the Expert Committee on Selection and Use of Medicines. A member of AsCSM presented a proposal for improving the presentation in applications for the EML of evidence on comparative safety. Given the varying backgrounds of applicants, who can be WHO departments, pharmaceutical companies, patient advocacy groups and many others, the Expert Committee noted that it would be difficult to satisfy all the possible requirements suggested in the proposal. The Expert Committee recommended that there should be collaboration between the two committees to improve the content of applications, the issues presented by the ASCSM will be considered in the process of modifying the ‘Information for applicants’ form.

On the basis of the experience of from several meetings since 2002, the Committee then discussed possible modifications to the currently available ‘information for applicants’ form. To enhance the quality of applications and ensure appropriate presentation of all relevant clinical evidence, the Committee suggested the following:

- Specifying minimum criteria for acceptance of applications for consideration by the Committee.
– A requirement for a consideration for both paediatric and adult data in all applications.
– Specification of active pharmaceutical ingredient dosage forms and strength in detail.
– Specification of more detailed information about the regulatory status of medicines proposed for inclusion.
– Clarification of the purpose for listing, i.e. whether and application is for an individual medicine or an individual medicine with a square box.
– Submission of evidence of comparative effectiveness and safety in tabular form, using GRADE tables where appropriate.

5. Review of missing essential medicines for HIV

The Committee reviewed a proposal from the UNITAID Secretariat and WHO regarding the identification of missing essential medicines for HIV. The proposal describes the initiative that the UNITAID Board has endorsed recommending the development of a patent pool as one mechanism for encouraging the development of new products to meet public health needs. Comments on the proposal were received from MSF including a proposed list of missing essential medicines for HIV (see Appendix 1). Expert reviews were prepared by Mr Gray and Dr Henkens.

The Committee welcomed the patent pool proposal as an example of a new initiatives to develop desirable new products. For example, the Committee has previously identified the need for the development of fixed dose combination products for HIV especially where they improve efficacy and adherence. They acknowledged the need for pediatric dosage forms as well. The Committee has also previously identified the need for additional classes of medicines for HIV and acknowledges research in developing new drugs in existing classes of medicines as well as in new classes. In developing the list of essential medicines to date, the Committee noted that a wide selection of fixed dose combination products was not available.

The Committee acknowledged lists of medicines it received for possible inclusion in a patent pool (see Appendix XX) and noted that these lists would need periodic revision and updating depending on the progress in clinical research and drug development. Inclusion in a patent pool or any other list of potentially desirable products does not guarantee that these products will be added to the EML or included in treatment guidelines. The requirements for listing in the EML are based on evidence for comparative effectiveness, safety and cost for specific products.

In its discussion, the Committee also noted the potential value of applying this approach to other major public health problems. Consideration of these will have to be on a case by case basis, assessing the scope and nature of the public health problem and the apparent utility of this approach (identification of priority missing products for a patent pool) for solving it.
6. Review of the report of the Second Subcommittee and of the provisional Second List of Essential Medicines for Children

1. General Issues

The Expert Committee considered the report of a recent meeting (October 2008) of the Expert Subcommittee (See PART TWO) and thanked them for the up-dated list of Essential Medicines for Children. The Expert Committee strongly supported the recommendation from the Subcommittee that in order to meet the critical needs of improving paediatric therapeutics throughout the world, WHO should create approaches to generate the new knowledge necessary for translation of discovery into rational therapeutic practices. The Committee endorsed the recommendations of the Subcommittee regarding clinical research and information gaps related to paediatric therapeutics, ranging from product availability to considerations of medicine selection and therapeutic use. Additional research priorities identified by the Committee were: pharmacokinetics studies in neonates, for example oral amoxicillin, effects of malnutrition on pharmacokinetics, medicines for resuscitation in neonates, and determining proper dosage, timing of drug administration in relation to food intake when relevant.

2. Review of key recommendations from the Subcommittee for the EMLc

The Committee noted the significant progress in the further development of the EMLc made by the Subcommittee and endorsed the addition of two new sections to the List: medicines for ear nose and throat disease and medicines specifically for neonatal care. These medicines are relevant for the pediatric population and will be included on the Complete EML.

The Committee recognized the high burden of disease occurring in neonates and young infants and accepted the proposal from the Subcommittee for the addition of an annex to the EMLc of medicines from the EMLc which are felt to be essential in treating a variety of neonatal conditions.

The Committee considered the recommendation of the Subcommittee that the EMLc remains separate from the "complete" EML for the foreseeable future. The "complete" EML will include the EMLc. Publishing two lists maintains a critical focus on the needs of children and supports advocacy for children's health. The Committee however, recognized the importance of having a combined list that could facilitate procurement. It recommended that in publishing the complete List, the WHO should identify those medicines that were included in it only for use in children with a new symbol.

The Committee discussed current inconsistencies between the two lists and agreed that it was important to harmonize them. This approach is reflected in the recommendations for additions and deletions to the Model List that were made at this meeting. The following inconsistencies were noted and resolved as follows:

- The Subcommittee recommended that the current use of sulfadiazine was only for treatment of toxoplasmosis and should therefore be deleted from Section 6.2.2 and
added to Section 6.4 in both the complete EML and EMLc. This recommendation was accepted by the Committee.

- The Subcommittee had considered an application for inclusion of fludrocortisone in Section 18 and recommended inclusion on the EMLc; the Committee noted that this would be essential for treatment of congenital adrenal hypoplasia and adrenal failure in adults as well as children and it was therefore added to the complete EML.

- The Subcommittee had recommended addition of cefalexin to the EMLc as an oral cephalosporin palatable for administration to children so it was added the EMLc. The Committed did not add it to the EML as palatability is less of a consideration in adults.

- The Subcommittee had recommended the addition of liposomal amphotericin B for visceral leishmaniasis, and the deletion of pentamidine for this indication as it was no longer used for this purpose in children. The Committee reviewed Section 6.5.2, medicines for leishmaniasis for concordance between the EML and EMLc and on the advice of the WHO Department of NTD, made the same changes to the complete EML.

- The Subcommittee had recommended the addition of a number of medicines for use in palliative care in children (Section 8.4) While noting that many of these medicines may also be used in adults, the Committee decided that at this time, further review of the specific medicines and dosage forms was needed to identify those most suitable for inclusion in the same section of the complete List for use in adults. The Committee requested that the Secretariat give this review high priority.

- The Subcommittee had moved caffeine citrate, indicated for use in the treatment of neonatal apnea, from Section 25.2 to Section 29 (medicines specifically for use in neonates.) The Committee agreed that this change should be made in the complete EML as well.

The Committee recognized the importance of coordinating the maintenance and further development of the two lists, for example, by requiring that use in children and adults be considered in every application to the EML. If the applicant leaves either aspect out, the Secretariat should request this to be addressed by the applicant or other party as appropriate.

3. Review of comments on the second EMLC

The Expert Committee reviewed comments that had been submitted to the Secretariat on the draft report of the Subcommittee published on the WHO website following the Subcommittee meeting.

Chlorhexidine solution

Following the inclusion of chlorhexidine solution to the EMLc by the 2nd Subcommittee for the Selection of Medicines for children, in October 2007, comments were received from PATH and USAID.

The Committee noted that the comments from both organizations expressed satisfaction with the inclusion of chlorhexidine but sought to inform the committee
about developments in the process of making the recommended 4% solution. The Committee noted that both PATH and USAID forecast the availability of the 4% solution in 2010, and that product specifications have been developed by PATH and are available to manufacturers. USAID pledged their support for this process.

The Committee decided to retain the 20% formulation until the 4% formulation becomes widely available. The Committee confirmed its current position of listing available dosage forms only.

**Comments on fluoroquinolones in children**

At the 2nd Subcommittee of the Expert Meeting in October 2008, the Subcommittee recommended retaining ciprofloxacin in the core list of the EMLc after concluding that sufficient evidence was available to support the use of ciprofloxacin as a second-line treatment for specific, severe infections in paediatric patients.

The Committee considered comments received from Dr D Fuller and Mr Hal Fisher of the Fluoroquinolone Toxicity Research Forum in response to this decision. The Fluoroquinolone Toxicity Research Forum is an advocacy group against the use of Fluoroquinolones. Both submissions contained general references to cases of permanent harm and to clinical trials to support the case against use of fluoroquinolones in children.

In addition to the information provided, the Committee reviewed the results of a literature review undertaken by the Secretariat. The purpose of the search was to identify new information on the safety of fluoroquinolones in children. Five review studies from 2003 to date, and 3 clinical trials from the same period were identified.

The main findings were:

- Ciprofloxacin is relatively safer than other fluoroquinolones (1, 2, 4).
- Fluoroquinolones are associated with arthropathy in children, which is reported to be of moderate intensity, but transient (1, 2, 3, 4).
- For some indications, i.e. shigellosis, and pseudomonas infections, fluoroquinolones are accepted therapies (1)

The Committee acknowledged the increasing prevalence of resistance to fluoroquinolones and the public health impact of a likely increase of pediatric rhinopharyngeal carriers of resistant pneumococci if use in this population is not restricted (1).

The Committee considered the risk-benefit balance of continuing to include ciprofloxacin on the EMLc. After giving due consideration to safety concerns and the issue of resistance, it noted that retaining it on the EMLc would allow its use in serious infections for which there is no satisfactory alternative treatment or when evidence supports that fluoroquinolones are the best option. The Committee
therefore decided to retain ciprofloxacin in the core list of the EMLc but a formal review of safety of ciprofloxacin and quinolones in children was requested.

**Review of entry of Budesonide MDI (paediatrics)**

**Section 25.1: Antiasthmatic medicines**

Comments on budesonide as listed in the draft 2nd edition of the EMLc were received from Cécile MACE, Asthma Drug Facility Coordinator, Quality Assurance Pharmacist, International Union Against Tuberculosis and Lung Disease

The Committee noted that Miss Mace had correctly pointed out the errors in the description of budesonide metered dose inhalers with reference to strengths and the salt "dipropionate".

The Committee approved the corrected version as below:

**25.1 Antiasthmatic medicines**

budesonide Inhalation (aerosol): 100 micrograms per dose
200 micrograms per dose.

The Committee noted the confusion arising from this error as to whether budesonide or beclometasone is the corticosteroid included in the EMLc, and confirmed that budesonide was chosen is it is more widely available.

**4. Conclusion of review of Subcommittee report**

In its report, the Subcommittee concluded that it had satisfied its terms of reference and recommended, in principle, that the Subcommittee be dissolved. The Expert Committee agreed and made the recommendation to the Executive Board and the Director-General that the Subcommittee had fulfilled their terms of reference regarding the development and revision of the WHO Model List of Essential Medicines for Children and should now be dissolved. Future Expert Committees should, however, include adequate expertise to consider medicines for children and maintain the EMLc. The Committee also recommended that given the number of reviews still required for sections of the EMLc, an Expert Committee meeting focused on these pediatric medicines should be held as soon as feasible.

**7. New applications for paediatric medicines**

**Section 6: Anti-infective medicines**

**Section 6.2: Antibacterials**

**Procaine benzylpenicillin (Review) -- (EMLc)**

This application was commissioned after the October 2007 meeting of the WHO Expert Subcommittee on the Selection and Use of Essential Medicines requested a review of the use of procaine benzylpenicillin in neonates. It was prepared by the WHO Collaborating Centre, Discipline of Clinical Pharmacology, Newcastle, Australia. Expert reviews of the application were prepared by: Dr E. Zisovska and Professor Dai Yao Hua.
The Committee noted that 98% of peri-natal mortality occurs in low income per capita, less developed and least developed regions of the world and 27% of perinatal mortality is due to neonatal sepsis (5, 6). 800,000 neonatal deaths occur annually from pneumonia in developing countries (7).

The Committee noted papers cited in the application that showed that in resource poor settings, families may be unable to access care for sick neonates (8), and that a study of a complex intervention including community based healthcare with regular visits by community based health worker, early referral and administration of i.m. procaine penicillin and gentamicin to treat infections in the community resulted in reduced mortality (9). While the overall reduction of 27% was recorded in neonatal mortality, it was not possible to extract the relative importance of procaine penicillin to this result.

The Committee noted that current clinical practice guidelines recommend the use of procaine penicillin in neonates exclusively for the treatment of asymptomatic congenital syphilis (10, 11, 12). One prospective RCT was cited that provides evidence that procaine penicillin is effective in the treatment of asymptomatic congenital syphilis in neonates, although it achieves lower CSF concentrations than i.m. benzylpenicillin (13). No data for efficacy of procaine penicillin alone for the management of neonatal sepsis were available. Pharmacokinetic studies cited showed that procaine penicillin takes up to 24 hours to peak in CSF and does not achieve comparable concentrations to i.m. benzyl penicillin (14, 15, 16).

The Committee noted the following concerns about use of procaine penicillin in neonates: that adverse effects are well described and include abscesses and neurological damage at the site of injection; and that the translation of the trials of complex interventions into the community may be hindered by a lack of compliance with safe injection practices; in the trials the community health care workers were trained and supervised in proper administration.

The Committee is aware of ongoing trials to further evaluate the role of procaine penicillin and other antibiotics with potentially more favourable adverse effect profiles, in the community based management of neonates with sepsis. The Committee will review the available data at its next meeting.

The Committee therefore considered whether to retain the current age restriction and note on the use of procaine penicillin. Given the potential mortality benefit in neonates with severe sepsis compared to the adverse effects, on balance the Committee decided to remove the age restriction, but amended the note to indicate restricted use:

"Procaine penicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable."

Section 6.2.4: Antituberculosis medicines (Review, EMLc)

At its first Subcommittee meeting, a note was inserted in Section 6.2.4 of the EMLc, requesting a review of the evidence for the doses and therefore strengths, of the first line medicines for TB in children, particularly the fixed dose combination products. This request
has initiated a programme of work by EMP and the Stop TB Department, WHO, that has included the following activities:

- A comprehensive review of the pharmacokinetic literature for isoniazid, rifampicin and pyrazinamide including studies in children (report by Peter Donald).
- A meeting in July 2008, to review this report and recommend on further actions needed (http://www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf).
- Consideration of the July meeting report at the Subcommittee meeting in October 2008, that lead to the recommendation for deletion of the existing low dose FDCs (for children) on the grounds of concerns about inefficacy.
- Two reports from simulation studies (agenda papers for this meeting) proposing potential new strengths for FDCs.
- A review of evidence for safety, especially hepatotoxicity, of isoniazid, rifampicin and pyrazinamide (Peter Donald).

Ongoing, but not yet complete activities are:

- A systematic review of evidence concerning use of, efficacy, safety and pharmacokinetics of the first line TB medicines in children less than 6 months of age (due end April 2009).
- A systematic review of the evidence for efficacy and safety of intermittent treatment regimens of TB in Children (due June 2009).
- Updating the WHO TB treatment guidelines for children; this process has commenced and is likely to be completed late this year.

The pharmacokinetic simulations that have been done suggest two FDCs that would produce levels of systemic exposure predictive of efficacy and safety in children from 5-30 kg assuming a single daily dose and not fractionating the tablet in more than half (dosing schedule is in the reports):

- a 3-drug FDC: isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg.
- a 4-drug FDC: ethambutol 250 mg + isoniazid 150 mg + pyrazinamide 400 mg + rifampicin 250 mg.

The review of the safety of these drugs in children suggest that these doses would be acceptable in terms of toxicity.

The Committee noted that at this time, there are no FDCs that deliver the ‘ideal doses’ of first line medicines for TB treatment in children between 5 and 30 kg. The Committee also noted a need for a 2 drug FDC for use in the continuation phase of treatment and recommended that
the following combination (for continuation treatment only) would be reasonable based on the analyses presented:

– isoniazid 150 mg + rifampicin 250 mg.

Products developed as fixed dose combination products must meet standards for quality and be in an appropriate dosage form for children. The Committee noted that the Secretariat had already consulted with manufacturers regarding the potential need to develop new products as soon as possible to meet the new ‘ideal’ specifications. The Committee encouraged the Secretariat to work with all relevant stakeholders to promote rapid development of the products and looks forward to their availability for assessment for the EML. The Committee endorsed the decision of the Subcommittee to delete the low dose FDCs from the EMLc and recommended that they also be deleted from the complete List.

Section 6.3: Antifungal medicines

Liposomal amphotericin B (Inclusion in the EMLc)

This application was commissioned by the WHO Secretariat following a request from the Subcommittee meeting in October to assess the evidence for efficacy and safety of liposomal amphotericin B for use for the treatment of fungal infections. The Subcommittee had recommended its inclusion for visceral leishmaniasis.

Expert review of the application was prepared by Dr Dodoo.

The application described that invasive fungal infections are increasing in prevalence globally, and that these infections are associated with high mortality rates (25 to 95%) in children. Several guidelines quoted in the application recommend the use of liposomal amphotericin B(LAB) as well as amphotericin B deoxycholate(ABD). The CDC, the National Institutes of Health, and the Infectious Diseases Society of America (17) guidelines for treatment of children with HIV/AIDS recommend the use of liposomal amphotericin B in patients with comprised renal function.

The Committee noted that some evidence submitted in the application supports the relative efficacy of LAB versus ABD. Twenty pediatric observational studies supported the efficacy and safety of LAB in children and neonates. LAB may be less nephrotoxic and is less likely to cause fevers and chills during administration than ABD, but not significantly different from ABD in terms of hepatotoxicity and reports of electrolyte imbalance.

On balance, the Committee recommended that the listing of amphotericin B be modified on both EML and EMLc to specify both the deoxycholate and the liposomal form. It would be up to countries to select which to use depending upon availability and cost. The Committee noted that the Formulary should include instructions about the lack of interchangeability of the two dosage forms.
Section 6.5: Antiprotozoal medicines

Section 6.5.3: Antimalarial medicines

Artemether + lumefantrine (Inclusion in the EMLc)

An application was prepared by I. Meyer for Novartis Pharma to include the dispersible formulation of artemether + lumefantrine 20 mg +120 mg in the EMLc. This formulation of the fixed-dose combination non-dispersible tablet is already included in the EML and the EMLc. The application seeks approval for the additional dosage form of "dispersible" tablets.

Expert reviews of the application were prepared by Dr How and Dr Dai Yao Hua.

The Committee noted that artemether + lumefantrine 20 mg + 120 mg is included in the WHO Guidelines for curative treatment of uncomplicated malaria (18). It is already included as the dosage formulation of "tablet" in both the EML and the EMLc.

The Committee acknowledged the therapeutic equivalence of the "dispersible" form supported by a multi-centred trial (N=899) conducted in malaria endemic regions of Africa (19). The Committee recommended the addition of the "dispersible" formulation of artemether + lumefantrine 20 mg + 120 mg to the Essential Medicines List for Children as a child friendly dosage form, to be used where available for children in the weight range of 5 kg to 30 kg.

Section 7: Antimigraine medicines

Ibuprofen (Inclusion in the EMLc)

This application was prepared for the organization Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide, by P. Tfelt-Hansen, Glostrup Hospital, Glostrup, Denmark, and T. Steiner, Chairman, Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide, Imperial College, London, UK. The application seeks the addition of ibuprofen tablets 200 mg to the EMLc as an anti-migraine medicine to enable convenient delivery of the dose 7.5 to 10 mg/kg to children 6 years and above.

Expert reviews were prepared by Dr E. Zisovska and Professor Dai Yao Hua.

The Committee noted that migraine presented an important public health concern for adults as well as children and adolescents (20). It results in significant loss of school days and interferes with education (21).

The Committee noted the studies cited in the application that support the efficacy of ibuprofen in the acute treatment of migraine in children compared with placebo and with paracetamol (22, 23). The Committee noted that ibuprofen 200 mg tablets are already included in the core list of the EMLc for migraine and recommended no further changes.
Section 12: Cardiovascular medicines

Section 12.4: Medicines used in heart failure

**Captopril (Inclusion in the EMLc)**

An application was prepared by Dr Sean Beggs, General Pediatrician & Pediatric Clinical Pharmacologist, Royal Hobart Hospital, Senior Lecturer, University of Tasmania in response to the Subcommittee’s request for a review of the section on medicines used in the treatment of heart failure in children.

Expert reviews of the application were prepared by Dr Kearns and Dr Zisovska.

The Committee noted that the application was supported by evidence of efficacy and safety of angiotensin converting enzyme inhibitors (ACE-I) from various adult studies. The causes and types of heart failure in children are significantly different from those in adults and the evidence of efficacy and safety of use of ACE-I in children are based on a few small observational studies. None of the studies done in children directly compare various ACE-I. The question of use these medicines in the treatment of hypertension was also discussed, noting that the current application did not address this directly.

The Committee considered whether to list enalapril or captopril as an indicative ACE-I, with a square box. There is slightly more evidence for efficacy and safety for enalapril and it is licensed by at least one stringent regulatory authority for use in children. The Committee noted that the EMEA may have further information available about this topic in the future, and suggested that WHO continue to collaborate with them as data become available.

On balance, noting that a flexible oral solid dosage form would be desirable, the Committee recommended the inclusion of enalapril in the EMLc for the treatment of hypertension in children, with the addition of the square box symbol.

**Carvedilol (Inclusion in the EMLc)**

This application was prepared by Dr Sean Beggs, General Paediatrician & Paediatric Clinical Pharmacologist, Royal Hobart Hospital, Senior Lecturer, University of Tasmania following a request by the Subcommittee. Expert reviews of the application were prepared by Dr Hoppu and Dr Kearns.

The application presented evidence from adult studies (24, 25, 26) to support the efficacy and safety of carvedilol in treating heart failure, and summarized studies published to establish the role of carvedilol in heart failure in children. The Committee noted that beta-blockers have major dose-related side-effects that may limit their use in children with severe heart failure (27).

Noting again that the causes and types of heart failure in children are significantly different from those in adults, the Committee decided that at present there was not enough evidence of comparative effectiveness and safety to justify inclusion of carvedilol in the complementary list of the EMLc.
Section 17: Gastrointestinal medicines

Section 17.2: Antiemetic medicines (Inclusion of ondansetron in the EMLc)

A review of the use of anti-emetics in children particularly for the treatment of post operative nausea and vomiting was prepared by the Discipline of Clinical Pharmacology, University of Newcastle, Australia, following a request by the 2nd Subcommittee. Expert reviews of the submission were prepared by Dr M. Reidenberg and Mrs J. Al-Fannah.

The Committee noted that data summarized in the submission showed that, of the anti-emetics available, those with the greatest evidence of efficacy in the prevention of post-operative nausea and vomiting (PONV) were ondansetron and dexamethasone. The use of promethazine in treatment of PONV was not supported by any published data.

The Committee noted the guidelines from the Society for Ambulatory Anesthesia (SAMBA) (28) that recommend ondansetron as first line treatment for prevention of PONV, with the addition of dexamethasone as required. Metoclopramide and promethazine are not currently recommended.

The Committee recognized that all the medicines for the prevention of PONV have age restrictions on use, with the exception of ondansetron which is licensed for use in children older than 1 month by the US FDA. Droperidol has a black box warning from the FDA due to its association with adverse cardiovascular effects (28). One review of trials in children showed a relative risk of 1.15 to 1.66 for adverse effects with droperidol, and the higher risks are associated with higher doses and longer exposure (29).

The Committee recommended the inclusion of ondansetron with a square box symbol and dexamethasone as an antiemetic on both the EML and EMLc. It recommended the retention of metoclopramide as an anti-emetic for children. It recommended that promethazine be deleted from the EML and EMLc due lack of efficacy in post operative nausea and vomiting. The Committee also noted that H1 blockers are effective for motion sickness, but did not consider this to be a public health priority.

Section 18: Hormones

Section 18.5: Insulins and other antidiabetic agents

Access to Essential Diabetes Medicines for Children in the Developing World

The Committee were provided with the report of the meeting on Access to Essential Diabetes Medicines for Children In the Developing World. The Committee noted with concern the activities of the Insulin for Life Prevention Centers in relation to collecting unused medicines for redistribution and recommended that the group adhere to WHO Guidelines for Drug Donations regarding use of expired medicines.
The Committee would welcome an application for inclusion of glucagon on the EML.


The original terms of reference for the Expert Subcommittee included determining suitability criteria for dosage forms of medicines for children, and considering the feasibility of manufacturing appropriate formulation for those priority medicines for which no dosage form exists.

At first meeting in October 2008, the Subcommittee reported that the work addressing suitability criteria for dosage forms was still incomplete. Subsequently, an informal expert consultation on dosage forms of medicines for children has been held (December 2008) and the report from that meeting is provided as an agenda paper for this Expert Committee. The literature review used as a background paper for that meeting is available on request; it is being prepared for submission for publication.

The report of the December meeting includes 10 proposed recommendations. Numerous comments have also been received on the report, and these have been posted on the web. Key general issues identified in those comments are:

- Lack of detailed discussion of regulatory issues.
- Whether there is sufficient consideration of the feasibility of manufacturing preferred dosage forms and the impact on dispensing.
- Whether there is sufficient consideration of commercial and market issues.

The Committee endorsed the report and decided to include it as (Appendix 2) to the Committee report in its current form. The Committee recognized the importance of the comments received on the report in stimulating discussion. The Committee requested that the Secretariat continue to develop the report in consultation with stakeholders with goal of having a revised report for review by this Committee, the Expert Committee on Pharmaceutical Specifications, and other relevant groups within WHO.

The Committee also considered extemporaneous preparations involving polypharmacy. The Committee noted that in 1985, the WHO defined rational use of medicines as requiring “patients receive medications appropriate to their needs, …...”. The custom in some places is to treat sick children with a mixture of several medicines (“puyer”), not necessarily all appropriate to their needs. Commonly, adult solid dosages forms are mixed together, ground to a powder, and the powder divided into assumed pediatric doses and then dispensed for administration to the child. Often, some medicines in the mixture are not indicated for the condition being treated. These medicines add to the risk of adverse events without any possibility of adding additional benefit. The Committee recommended that as this practice is irrational it should not be used.
9. Applications for the 16th Model list

Section 4: Antidotes and other substances used in poisonings

Section 4.2: Specific

Pralidoxime (Inclusion)

An application for the inclusion of pralidoxime was prepared by the Department of Clinical Pharmacology, School of Medicine and Public Health, Faculty of Health, University of Newcastle, New South Wales, Australia. The application was commissioned by the Secretariat.

Expert reviews of the application were prepared by: Professor Noel Cranswick, Professor Elizabeth Zisovska and Prof How. Comments were received from Ms Joanna Tempowski, Scientist, Chemical Safety, Department of Protection of the Human Environment, WHO.

The Committee noted that the application provided a thorough review of the available evidence regarding the efficacy and safety of pralidoxime given to adults for the treatment of organophosphate poisoning. It was noted by all expert reviewers that available evidence does not support that pralidoxime treatment alone represents an effective antidote for acute organophosphate poisoning in adults. This opinion was supported by considering five systematic reviews of multiple studies, both controlled and uncontrolled. The Committee noted several challenges with the interpretation of existing data from adult studies such as inconsistency in pralidoxime dose and method of administration, time of onset of treatment related to the ingestion/exposure to the organophosphate and concomitant use of other treatments for organophosphate poisoning (e.g., atropine sulfate, early mechanical ventilation). The Committee also noted that there are existing data from several small pediatric case series, not cited in reviews included in the application, where continuous intravenous infusion of pralidoxime at doses higher than those reported from many adult studies appeared to be associated with efficacy and safety (30). The Committee is aware of an additional large study that is not yet reported (31).

The Committee agreed that the majority of evidence from the studies in adults suggests that the efficacy of pralidoxime, as used in these studies, is not demonstrated. The Committee recognized the need for further research to evaluate the impact of dosing regimens for both pediatric and adult patients, the effect on different organophosphates, and the potential efficacy and safety of different oximes. The Committee also noted that pralidoxime is comparatively expensive. On this basis, the Committee recommended that pralidoxime should not be added to the WHO Essential Medicine List at this time.

Section 5: Anticonvulsants/antiepileptics

Lamotrigine (Inclusion)

An application was submitted by CeVEAS, NHS Centre for the Evaluation of Effectiveness of Health Care, World Health Organization Collaborating Centre for Evidence Based Research
Synthesis and Guideline Development in Reproductive Health, Modena, Italy for the addition of lamotrigine as monotherapy for the treatment of new onset partial epilepsy in patients not tolerating carbamazepine and for the treatment of new onset generalized epilepsy in women who are contemplating pregnancy. Listing was proposed as an individual medicine.

Expert reviews of the application were prepared by Dr G. Batmanabane and Dr E. Narváez Delgado. Comments in relation to the application were received from Dr B. Saraceno, Director, Department of Mental Health and Substance Abuse, WHO.

The Committee noted that the application provided a comprehensive and systematic review of all the available evidence for the efficacy and safety of lamotrigine for epilepsy in adults. The Committee noted that evidence for its efficacy and safety in children is very limited.

The evidence supporting the use of lamotrigine in new onset partial epilepsy came from 1 pragmatic RCT of moderate quality (32), 1 systematic review of 4 short-term RCTs of moderate quality (33) and a further 4 short-term RCTs with quality ranging from moderate to very low (34, 35, 36, 37). Overall the results were not conclusively in favour of lamotrigine. Carbamazepine was found to be superior to lamotrigine in terms of efficacy outcomes (seizure freedom in short-term follow up and time to first seizure in long-term follow up).

The Committee were concerned that the evidence of effectiveness and safety for the use of lamotrigine in pregnant women is currently limited and of a conflicting nature. They noted that data presented in the application from two recent epidemiological studies suggest that the risk of orofacial cleft may be higher among offspring of women treated with LTG during pregnancy (38, 39).

The Committee did not recommend the inclusion of lamotrigine to the Model list based on the lack of evidence of its superior efficacy and safety and cost-effectiveness compared to comparators, and the availability of suitable alternative first-line antiepileptics which are already on the Model List. The Committee recommended a review of second-line antiepileptics for a future meeting, including a review of topiramate, lamotrigine and gabapentin as a second-line therapy for children and adults.

Addition of lorazepam and midazolam

An application was submitted by Professor Emilio Perucca, Head, Clinical Trial Centre, Institute of Neurology IRCCS C Mondino Foundation and Professor of Medical Pharmacology, Department of Internal Medicine and Therapeutics, University of Pavia, Italy, for the addition of parenteral lorazepam (2 mg/ml; 4 mg/ml) for the intravenous treatment of prolonged convulsive seizures and status epilepticus in children and adults and the addition of parenteral midazolam (5 mg/ml) for buccal administration for the treatment of repetitive and prolonged convulsive seizures, including status epilepticus where IV access is unavailable, in both children and adults. Listing in each case is as an individual medicine and formulation.
Expert reviews of the application were prepared by: Dr E. Narváez Delgado and Dr G. Batemanabane. Comments supportive of the application were received from Dr B. Saraceno, Director, Department of Mental Health and Substance Abuse.

The Committee noted that the application included a comprehensive summary of all the available evidence for the effectiveness and safety for parenteral lorazepam and parenteral midazolam for buccal administration for the treatment of prolonged convulsive seizures and status epilepticus in children and adults.

**Lorazepam (Inclusion)**

The Committee noted that the evidence presented in the application to support the superior effectiveness and safety of lorazepam compared to a range of other drug treatments for status epilepticus in adults and children came from two Cochrane Reviews (40, 41) and five randomized comparative trials of parenteral lorazepam (42, 43, 44, 45, 46). Overall the evidence showed that lorazepam was at least as effective as diazepam and had fewer adverse effects when used for the management of status epilepticus.

The Committee recommended the inclusion of parenteral lorazepam with a square box to replace diazepam on the Model List based on its comparative effectiveness and safety when compared to other medicines for the management of prolonged convulsive seizures and status epilepticus in adults and children. The rectal formulation of diazepam was maintained because it is a commercially available preparation and offers an option for treatment of severe seizures in patients when intravenous access is not available.

**Midazolam (Inclusion)**

The Committee noted that the evidence presented in the application to support the superior effectiveness and safety of buccal midazolam compared to rectal diazepam came from one Cochrane Review (1), three RCTs (47, 48, 49) and 1 quasi-randomized trial (50). The Committee noted that although the evidence for effectiveness was from studies in both high-income and resource poor countries, the majority of the evidence for efficacy and safety had been generated from use in Accident and Emergency departments and not at community level. The Committee also noted that buccal midazolam is not available in many countries and parenteral midazolam is currently not licensed for buccal use in acute seizure disorders. Parenteral midazolam is only licensed for use for sedation and anaesthesia.

The Committee did not recommend the addition of parenteral midazolam to the Model List at this time due to the lack of a substantial body of evidence to show its effectiveness and safety in community settings for seizures, and the availability of a suitable alternative already on the Model List.
Section 6: Anti-infective medicines

Section 6.2: Antibacterials

Section 6.2.4: Antituberculosis medicines

**Rifabutin (Inclusion)**

An application was submitted by Dr Reuben Granich, Medical Officer (HIV/TB), Department of HIV/AIDS, WHO for the inclusion of rifabutin 150 mg capsule for the treatment of tuberculosis in HIV-infected patients treated with a concomitant ritonavir-boosted protease inhibitor. Listing was requested as an individual medicine as part of the therapeutic group of antituberculosis therapy.

Expert reviews of the application were prepared by: Professor Dai Yao Hua and Professor Cleotilde Hidalgo How.

The Committee noted that rifamycins are an essential component of modern short-course regimens for treating tuberculosis and antiretroviral therapy (ART) in combination with WHO-recommended DOTs is an essential component of TB control and significantly improves survival in HIV/TB co-infected patients. Ritonavir-boosted protease-inhibitor (PI) based ART is recommended by WHO as the preferred second-line therapy for HIV infected individuals or as an alternative option in those with adverse reactions or contraindications to NNRTIs used in standard first-line therapy. Under normal circumstances rifampicin is the recommended rifamycin in modern standard TB therapy; however rifampicin interacts with protease inhibitors leading to sub-therapeutic concentrations of protease inhibitors mediated by CYP3A4. In contrast, rifabutin has little effect on PI serum concentrations allowing the concomitant use of rifabutin and ritonavir-boosted PIs.

The evidence presented in the application to demonstrate the comparative effectiveness and safety of rifabutin versus rifampicin for the treatment of TB was based on a Cochrane Review (51) (5 RCTS, 924 patients). The review found that there was no difference in terms of efficacy between rifabutin- and rifampicin-containing regimens as assessed by sputum culture conversion at two, three, or six months on treatment. However, the Committee noted that HIV-positive people were under-represented in the included trials. The only comparative RCT in HIV positive patients included in the review found both rifamycins to be safe and effective and demonstrated more rapid clearance of acid-fast bacilli in the rifabutin arm (52).

The Committee acknowledged that evidence presented in the application from observational cohort studies including HIV-infected patients treated with ART did not point to an inferior performance of rifabutin. The Committee noted that according to a cost-analysis of PI-based ART with rifampicin or rifabutin based TB regimens, undertaken in March/April 2007, the total combined cost of HIV and TB therapies using rifabutin was cheaper than that with rifampicin.
The Committee recommended that rifabutin was added to the core Model List based on the public health need, evidence of equivalent efficacy and safety compared to rifampicin for the treatment of TB, and the fact that it has little effect on PI serum concentrations allowing the concomitant use of rifabutin and ritonavir-boosted PIs in HIV infected individuals requiring second-line ART and treatment of tuberculosis.

Section 6.4: Antiviral medicines

Section 6.4.2: Antiretrovirals

Atazanavir (Inclusion)

An application has been prepared by Dr Patti Whyte, on behalf of the Department of HIV for the inclusion of atazanavir (ATV), 100 mg and 300 mg capsules, for the treatment of HIV-1 infection in adults on the Model List. Expert reviews were prepared by Dr Lennita Wannmacher and Professor Anita Zaidi.

The Committee noted the application provided a comprehensive review of all the currently available evidence for the use of atazanavir (unboosted and boosted with ritonavir) in the treatment of HIV-1 infection in adults. A working group convened by WHO in 2007 (53) to develop guidance for second-line drugs, ranked atazanavir boosted with ritonavir as one of the highest priorities for the protease inhibitor component of second-line treatment.

The Committee noted that the application provided evidence from a large number of RCTs (54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70) to support the comparable efficacy of atazanavir, either alone or in combination with ritonavir or other antiretroviral agents versus appropriate comparators for both the first-line and second-line treatment of HIV-1 in adults. Overall, the results indicated that atazanavir unboosted and boosted is an effective PI with a low pill burden. In second-line treatment, boosted ATV appeared to be more efficacious than unboosted ATV. For all the studies which reported lipid outcomes the atazanavir groups had significantly lower changes in lipid levels than the comparison groups.

The Committee noted that there was limited direct evidence of the efficacy of ATV in populations in resource-poor countries. However, evidence from a meta-analysis of antiretroviral treatment programs in resource-poor settings (71) included in the application demonstrated efficacy rates similar to those reported for developed countries for first-line treatment regimens. The Committee acknowledged that although the meta-analysis did not specifically access second-line treatment it was still probably reasonable to conclude that the efficacy of ATV is likely to be similar across developed and resource-poor countries.

The Committee noted that ATV use is associated with a number of adverse effects, in particular hyperbilirubinaemia that is of uncertain clinical significance. Overall, the evidence presented in the application indicated that ATV is well-tolerated, with an occurrence of adverse reactions similar or of a lower frequency than comparator PIs.

The Committee noted that the advantages of atazanavir are its simplicity of administration (once daily dosing) and its less undesirable effect on lipid profile compared to other PIs.
Once daily dosing may improve adherence on a long-term basis which was seen as a significant advantage by the Committee, since there is evidence that incomplete adherence to modern HAART over time is strongly associated with increased mortality (72).

The Committee recommended the inclusion of atazanavir to the Model List and EMLc based on the evidence of the comparable virologic efficacy of ATV + rtv with LPV/r and other PIs, an acceptable safety profile including a less undesirable effect on lipid profile compared to other PIs, and the advantage of once daily dosing.

**Protease inhibitors (Review)**

At its 15th meeting in March 2007, the Expert Committee recommended a review of Section 6.4.2.3, protease inhibitors, to reflect changes in treatment guidelines, use and availability of these medicines. The Department of HIV prepared the review for the Committee.

Expert reviews were provided by Mr Gray and Dr Zaidi.

The Committee noted that this is not a standard data-driven application, evaluated it taking account of other WHO materials and accessible evidence. The proposals included:

A. To remove all formulations of nelfinavir (NFV) from the EML.

B. To add the heat-stable fixed-dose combination (FDC) formulations of lopinavir/ritonavir (LPV/r 200 mg + 50 mg and 100 mg + 25 mg tablets) to the EML, while retaining the existing listing of formulations that require refrigeration (133.33 mg +33.33 mg capsules and 400 mg+100 mg/5 ml oral solution) until these have been replaced in most markets.

C. To remove the 200 mg and 333 mg tablet formulations of indinavir (IDV) from the EML.

D. To remove the 200 mg hard gel capsule formulation of saquinavir (SQV) from the EML, and to replace this with the 500 mg tablet formulation, but noting that this is to be used particularly for the treatment of tuberculosis co-infected HIV patients where concomitant use of a protease inhibitor with rifampicin is unavoidable.

E. To consider a separate application for the inclusion of atazanavir (ATV).

F. To add the heat-stable formulations of ritonavir (RTV 100 mg and 25 mg tablets) to the EML, while retaining the existing listing of formulations that require refrigeration (100 mg capsule and 400 mg/5 ml oral liquid) until these have been replaced in most markets.

G. To remove the 40 mg tablet formulation of stavudine (d4T) from the EML.

H. To add the FDC formulation of zidovudine/lamivudine/abacavir (ZDV/3TC/ABC 300 mg + 150 mg + 300 mg) to the EML.

It was noted that request G deals with the listing of a nucleoside reverse-transcriptase inhibitor (NRTI) and not a protease inhibitor. Items E and H are dealt with separately.
The evidence for the suggested removal of the 40 mg adult dose of d4T was provided in an addendum to the 2006 WHO Guidelines on Antiretroviral Therapy for HIV Infection in Adults and Adolescents (73). Data were reviewed from 3 sources (74, 75, 76). The evidence and recommendation was summarized as follows:

“A systematic review of nine randomized trials and six observational cohort studies strongly suggests that stavudine-containing regimens maintain clinical and virologic efficacy when stavudine is dosed at 30 mg twice daily, and that this reduced dose is associated with lower rates of toxicity, especially peripheral neuropathy, compared to the 40 mg twice daily dose. Complementary studies have also demonstrated a significant reduction of mitochondrial DNA depletion in patients on the 30 mg twice daily dose. However, there are limited data available about reducing the incidence of lactic acidosis with this strategy. Based on available evidence, the Guidelines Development Group has concluded that the 30 mg formulation of stavudine, dosed twice daily, should be used for all adult and adolescent patients, irrespective of body weight. This recommendation, which was previously considered an option, is now established as the preferred approach when d4T is used as part of an ARV therapeutic regimen."

The Committee considered the review by Mr Gray and recommended that:

A. That all formulations of nelfinavir (NFV) be removed from the EML on the basis of non-availability and reduced need for this medicine as part of a comprehensive antiretroviral treatment (ART) programme.

B. That the heat-stable fixed-dose combination formulations of lopinavir/ritonavir (LPV/r 200 mg + 50 mg and 100 mg + 25 mg tablets) be added to the EML, while retaining the existing listing of formulations that require refrigeration (133.33 mg + 33.33 mg capsules and 400 mg+100 mg/5 ml oral solution) until these have been replaced in most markets.

C. That the 200 mg and 333 mg tablet formulations of indinavir (IDV) be removed from the EML on the basis that these formulations are not needed as part of a comprehensive antiretroviral treatment (ART) programme.

D. That the 200 mg hard gel capsule formulation of saquinavir (SQV) be retained and the 500 mg tablet formulation be added, as this dosage form is required (though not the most desirable option) for the treatment of tuberculosis co-infected HIV patients where concomitant use of a protease inhibitor with rifampicin is unavoidable.

E. That the heat-stable formulations of ritonavir (RTV 100 mg and 25 mg tablets) to the EML, while retaining the existing listing of formulations that require refrigeration (100 mg capsule and 400 mg/5 ml oral liquid) until these have been replaced in most markets.

F. That the 40 mg tablet formulation of stavudine (d4T) be removed from the EML, on the basis of its safety profile and to ensure consistency with WHO guidelines.
**Fixed-dose combinations**

**Zidovudine + lamivudine + abacavir (Inclusion) (AZT/3TC/ABC)**

An application was submitted by Dr Patti Whyte on behalf of the Department of HIV for the inclusion of the combination tablet zidovudine/lamivudine/abacavir (AZT/3TC/ABC) for the treatment of HIV infection. Listing was requested as a fixed dose combination of the antiretrovirals group, including three nucleoside reverse transcriptase inhibitors.

Expert reviews of the application were prepared by: Dr Lennita Wannmacher and Professor Anita Zaidi.

The Committee noted that the quality application provided a comprehensive overview of all the currently available evidence regarding the safety and efficacy of this fixed-dose combination therapy for the treatment of HIV infection in adults.

The Committee noted that the evidence presented in the application provided conflicting results regarding the efficacy of AZT/3TC/ABC. A systematic review (77), which assessed triple combination therapy in antiretroviral-naive HIV-infected adults, found that triple NRTI regimens including AZT/3TC/ABC were virologically inferior to NNRTI and ritonavir-boosted PI-based regimens. One double blind RCT (78) demonstrated that AZT/3TC/ABC was virologically inferior to regimens including efavirenz, such that the AZT/3TC/ABC arm of the trial was halted. A retrospective database review (79) comparing AZT/3TC/ABC and AZT/3TC/EFV concluded that AZT/3TC combined with EFV was superior to AZT/3TC/ABC. All the other trials presented in the application indicated that AZT/3TC/ABC was non-inferior to the comparator regimen.

The Committee noted that although there is some evidence from RCTs (80, 81) to show that the fixed-dose combination AZT/3TC/ABC causes fewer symptoms of lipodystrophy and presented a more favourable lipid profile when compared to other ART regimens, there are some safety concerns with the use of abacavir.

Abacavir has been associated with serious and sometimes fatal hypersensitivity reactions in patients. Across the available trials, suspected hypersensitivity reactions occurred more frequently in the AZT/3TC/ABC treatment groups compared to combination regimens not including abacavir (81, 82). Evidence from a recent large multi-cohort study (83) has also shown an excess incidence of myocardial infarction in patients treated with abacavir.

The Committee acknowledged that the fixed dose triple combination AZT/3TC/ABC is comparatively more expensive than a double combination AZT/3TC plus abacavir. Median prices per patient per year in low-income countries are US$ 852 versus US$ 450 respectively. Under the same conditions, AZT/3TC/ABC is also more expensive than the current preferred triple combination ATZ/3TC/EVZ (US$ 322) for the initial treatment of HIV infection (84).

The Committee did not recommend the addition of this new FDC to the Model List due to a lack of specific evidence of the superior efficacy of AZT/3TC/ABC fixed-dose combination.
Where the combination is needed in individual cases, it can be achieved with the medicines already listed.

**Section 6.4.3: Other antivirals**

**Amantadine and rimantadine, oseltamivir, zanamivir (Inclusion)**

Applications for the inclusion of four antiviral medicines: amantadine, rimantadine, oseltamivir and zanamivir were commissioned by the Secretariat after discussion with the WHO Department of Global Influenza Preparedness. This follows collaboration between EMP and GIP since 2006, on preparing treatment guidelines for pandemic influenza, and developing strategies to enhance access to antiviral medicines in the context of developing plans for pandemic preparedness.

Expert reviews were provided by Dr R. Fernandopulle and Dr M. Henkens.

The applications summarize the public health issues in relation to pandemic influenza. The WHO treatment guidelines for human infection with H5N1 disease were published in 2006 and have been reviewed every year since initial publication. There has been no significant change to the recommendations. Oseltamivir or neuraminidase inhibitors remain the first choice of treatment in the context of non-pandemic H5N1 infection. However, in the past year there have been increasing reports of H1N1 resistance to oseltamivir (85). The case for combination treatment as the primary recommendation is therefore likely to be re-examined.

The Committee noted that all four applications provide comprehensive summaries of evidence, based on the GRADE profiles and updated searches that have been used in the guideline development process. The clinical evidence is based primarily on the systematic reviews published by Jefferson et al 2006 (86, 87).

The Committee considered that for the adamantanes, there is more evidence to support the use of amantadine than rimantadine in the prophylaxis and treatment of seasonal influenza, but only 8 case reports of use of amantadine in patients with confirmed H5N1 infection. The benefits in treatment of patients with seasonal influenza are limited to reduction in symptoms; there are no data on influenza related mortality. For the neuraminidase inhibitors, the Committee noted that there are 4 trials of oseltamivir and 7 trials of the use of zanamivir in treatment of seasonal influenza that suggest reduction in duration of symptoms. The confirmed human cases of H5N1 treated with oseltamivir were summarised in the application. There has been no published report of use of zanamivir.

There is one small RCT of combined treatment with inhaled zanamivir and rimantadine, compared with rimantadine alone, in hospitalized patients with serious influenza (88). There were no differences in effects between treatment groups. There has been considerable discussion in the literature about the need to develop combination treatments for influenza given the rapid development of resistance, but as yet there are no other clinical trials that can be used as the basis for a recommendation.

The Committee noted that the costs of amantadine and rimantadine vary but are generally cheaper than the neuraminidase inhibitors. Overall the evidence to support the effectiveness
of any of the four antivirals for treatment of avian influenza remains very low quality. The effect of these medicines on seasonal influenza is better established, but may be of less importance. When used for treatment of individual cases of H5N1, the cost is low but in the context of seasonal influenza, they have not been accepted as cost effective. On balance, the potential advantage of the inclusion of any of them on the List would be to perhaps increase availability and decrease price. This would be critical in the context of responding to a pandemic, but the pandemic preparedness plans already include stockpiling of antivirals (often donated.) It is not clear that addition of the medicines to the List would enhance this access program.

After consideration of these factors, the Committee recommended not including any of the antivirals on the List at the present time. However the Committee endorsed the proposal for an emergency meeting mechanism to consider one or more, including for paediatric use, should a pandemic occur.

Section 6.5: Antiprotozoal medicines

Section 6.5.5: Antitrypanosomal medicines

**Nifurtimox + eflornithine (Inclusion)**

An application was prepared by the Drugs for Neglected Diseases initiative (DNDi), for the inclusion of inclusion of nifurtimox for use in addition to eflornithine as combination therapy (NECT) regimen for treating stage 2 Human African Trypanosomiasis (HAT).

An expert review of the application was prepared by Dr Andy Gray and comments in support were received from 5 organizations and 2 WHO departments (The Institute of Tropical Medicine, Belgium; Eastern Africa Network for Trypanosomiasis, Tanzania; the Dept of Pharmaceutical Medicines, Swiss Tropical Institute, Basle, Switzerland; Médecins Sans Frontières; National HAT Control Programme, Ministry of Health Democratic Republic of Congo; Director, WHO Collaborating Center for African Trypanosomiasis Treatment Failure and Drug Resistance; Department of Control of Neglected Tropical Diseases, WHO; UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training In Tropical Diseases (TDR), WHO)

The Committee noted that 2nd Stage HAT is invariably fatal, and that 60 million people are estimated to be at risk, in endemic areas (Harhay et al. submitted for publication). Nifurtimox is already recommended in WHO (89) and MSF (90) Guidelines for use in treating HAT as second line treatment, given as oral monotherapy for 60 days.

The application was based on 2 small published and one unpublished study (91, 92, 93). The Committee accepted that the new regimen was not inferior to eflornithine monotherapy and less likely to be interrupted due to adverse events. The Committee noted that melarsoprol is unacceptably toxic (94), and is associated with a high rate of resistance (95, 96). The comparisons of procurement costs suggest that NECT is half as expensive as eflornithine monotherapy. The Committee noted that specific data concerning children was not available.
The Committee noted that trials in this disease are difficult to conduct, because of toxicity and cost and difficulty of administration of existing treatments as well as challenges in follow up and outcome assessment (requiring lumbar puncture). Recognizing the severity of the disease and the toxicity of existing treatment, the Committee recommended the inclusion of nifurtimox in Section 6.5.5 (for use in the NECT protocol). Post marketing surveillance is strongly recommended. A review of melarsoprol in the treatment of Trypanosoma brucei gambiense is proposed.

**Section 7: Antimigraine medicines**

**Sumatriptan (Inclusion)**

In 2007, the Expert Committee rejected an application for the inclusion sumatriptan on the Model List on the basis that the evidence provided did not demonstrate the superior comparative effectiveness, safety and cost-effectiveness of sumatriptan versus the currently available medicines for the treatment of acute migraine on the Model List.

An revised application has been submitted on behalf of Lifting The Burden: the Global Campaign to Reduce the Burden of Headache Worldwide by: P. Tfelt-Hansen, Consultant in Neurology, Chairman, International Headache Society Standing Committee on Clinical Trials, Danish Headache Centre, Department of Neurology, University of Copenhagen, Glostrup Hospital, Glostrup, Denmark, for the inclusion of sumatriptan 50 mg in the Model List as a second-line treatment for acute migraine. Listing is requested as an individual medicine, not as a representative of its class. The application also proposes that paracetamol for the treatment of migraine should be deleted from the Model List.

Expert reviews of the application were prepared by: Mrs J. Al-Fannah and Dr G. Batmanabane. Additional comments were received from Dr B. Saraceno, Director, Department of Mental Health and Substance Abuse.

The Committee noted that the application did not systematically review and present all the available evidence to support the comparative safety and effectiveness of sumatriptan for the treatment of acute migraine. High-quality clinical evidence does support the superiority of sumatriptan for the acute management of migraine compared to placebo (97). Evidence from a further six RCTs,(98, 99, 100, 101, 102, 103) published since the Cochrane review for sumatriptan was last updated, was reviewed by the Committee. Results from these trials showed that sumatriptan was at best equivalent to comparators; in two instances it was possibly inferior. The Committee noted that all the studies were undertaken in high-income western countries.

The Committee noted that there is currently insufficient evidence to support the use of sumatriptan as a second line medicines in petinets who do not respond to aspirin. The evidence presented in the application for this indication came from two small open-label treatment studies of eletriptan, rather than sumatriptan (113 and 110 patients with migraine respectively; no comparison group)(104, 105).

Given that the comparative efficacy, safety and cost effectiveness of sumatriptan versus other triptans and aspirin was not established, the Committee recommended that sumatriptan not
be added to the Model List. The Committee suggested a review of more data on effects of triptans in patients who do not respond to first-line therapy.

The Committee decided that the deletion of paracetamol from this section would only be considered if a formal application is submitted for review. The application would need to provide a systematic and comprehensive summary of all the available evidence to support the claims of a lack of efficacy and safety paracetamol for the treatment of acute migraine.

Section 8: Antineoplastic, immunosuppressives and medicines used in palliative care

Section 8.2: Cytotoxic medicines

**Carboplatin (Inclusion)**

An application has been submitted by the WHO Collaborating Centre, University of Newcastle, Australia for the inclusion of carboplatin for the treatment of advanced ovarian cancer. The application was commissioned by the Secretariat on the recommendation of the International Network for Cancer Treatment and Research.

An expert review of the application was prepared by Dr Marcus M. Reidenberg.

The Committee noted that the application included supportive evidence for the effectiveness and safety of carboplatin from systematic reviews (106, 107, 108) and RCTs (109, 110, 111).

The Committee noted that the most recent meta-analysis came from a Cochrane Review (108) which showed that carboplatin was no more or less effective than cisplatin in any particular subgroup of women with advanced ovarian cancer.

The Committee noted that the toxicity profiles of carboplatin and cisplatin are different, with carboplatin being better tolerated overall than cisplatin. The major dose-limiting adverse effects associated with carboplatin are thrombocytopenia and leukopenia; with cisplatin they are nephrotoxicity, ototoxicity, neurotoxicity and emesis.

The Committee noted that the evidence presented in the application indicated that carboplatin was more cost-effective than cisplatin.

Overall, the evidence provided in the application supports the public health need, comparable effectiveness and generally more favourable tolerability of carboplatin than cisplatin. The Committee therefore recommend that carboplatin replace cisplatin on the complementary Model List (with a square box) for the treatment of advanced ovarian cancer.

**Hydroxycarbamide (Inclusion)**

An application was submitted by WHO Collaborating Centre, University of Newcastle, Australia for the inclusion of hydroxycarbamide on the Model List Listing is requested as an individual medicine. The application was commissioned by the Secretariat on the recommendation of the International Network for Cancer Treatment and Research.
The application focused on the use of hydroxycarbamide in the treatment of adults with chronic myeloproliferative disorders: chronic myelogenous leukaemia (CML), essential thrombocythemia and polycythaemia vera, and head and neck cancer.

Expert reviews of the application were prepared by: Professor Abdol Majid Cheraghali and Professor Noel Cranswick.

The Committee noted that the application presented evidence from meta-analyses (112, 113) and clinical trials (114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127) which included relevant RCTs and observational studies, to support the use of hydroxycarbamide in the treatment of adults with chronic myeloproliferative disorders: chronic myelogenous leukaemia (CML), essential thrombocythemia and polycythaemia vera, and head and neck cancer.

The Committee noted that although the evidence for the cost-effectiveness of hydroxycarbamide is generally limited, there is some evidence from economic evaluations using hydroxycarbamide as a comparator which suggest it is the treatment of choice if the cost of the newer comparator is prohibitively expensive or if the newer treatment is not tolerated well by the patient.

The Committee recommended the inclusion of hydroxycarbamide on the complementary Model List, based on its role in multiagent chemotherapy and radiotherapy regimens for advanced squamous cell head and neck cancer, evidence to support its effectiveness and safety as an alternative treatment to interferon-α in the treatment of CML, and evidence to support its role in the treatment of high-risk patients with essential thrombocythemia. The Committee recommended the inclusion of a wide range of dosage strengths because the dosage must be calculated for each patient individually and must be based on body weight.

**Ifosfamide (Inclusion)**

An application was submitted for the inclusion of ifosfamide on the Model List by the WHO Collaborating Centre, University of Newcastle, Australia on the recommendation of the International Network for Cancer Treatment and Research. The application focused on the use of ifosfamide in the treatment of individuals with soft tissue and bone sarcomas, non-Hodgkin’s lymphoma, cervical cancer, ovarian cancer, and testicular germ cell tumours.

Expert review of the application was prepared by Professor Noel Cranswick.

The Committee noted that the application provided a comprehensive review of the available evidence for the use of ifosfamide in multiagent chemotherapy regimens for a range of different cancer types. Evidence from meta-analyses, (128, 129,130) RCTs (131, 132, 133) and observational studies (134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146) was cited to support the use of ifosfamide as part of a multi-agent chemotherapy regimen for the treatment of individuals with soft tissue and bone sarcomas, non-Hodgkin’s lymphoma, cervical cancer, ovarian cancer, and testicular germ cell tumours. However, the committee noted that overall the evidence from systematic reviews and RCTs was not conclusive to support the use of ifosfamide-combination chemotherapy regimens in the treatment of solid...
tumours and that although a large number observational studies demonstrated reasonable response rates, there was no overall benefit in terms of survival.

The Committee noted that ifosfamide is recommended as an integral component of several regimens by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Where alternatives are stated for the treatment of certain cancer types, these chemotherapy agents are already listed on the Model List.

The Committee recommend the inclusion of ifosfamide on the complementary Model List given the wide range of cancers for which this medicine can be used.

**Mesna (Inclusion)**

An application was submitted by the WHO Collaborating Centre, University of Newcastle, Australia for the inclusion of mesna for the prevention of oxazaphosphorine-induced haemorrhagic cystitis. Proposed formulations for inclusion were: tablets 400 mg; 600 mg and injection 400 mg/4ml; 1g/10 ml. The application was commissioned by the Secretariat on the recommendation of the International Network for Cancer Treatment and Research.

An expert review of the application was prepared by Professor Noel Cranswick

The Committee noted that mesna was developed as a specific chemoprotective compound against acrolein-induced bladder toxicity, a dose-limiting side-effect of both cyclophosphamide and ifosfamide.

The Committee noted the good quality of the application, which provided a comprehensive review of the available evidence. The application cited nine RCTs, of which five trials (147, 148, 149, 150, 151) showed that mesna was effective in reducing the incidence of haemorrhagic cystitis in patients receiving ifosfamide and/or cyclophosphamide as part of a multiagent chemotherapy regimen. It was noted by the Committee that all these studies were small and of poor quality. The remaining four trials (152, 153, 154, 155) did not show mesna prophylaxis to be effective. The three largest RCTs (between 100 to 200 patients) showed that mesna was not effective in preventing haemorrhagic cystitis or moderate-severe haematuria in patients receiving a cyclophosphamide-based chemotherapy regimen.

The Committee acknowledged that the evidence for the efficacy of mesna in reducing the incidence of urotoxicity associated with ifosfamide and/or cyclophosphamide chemotherapy was not conclusive. Although the current evidence is equivocal, the current standard of care is that mesna is used as an adjunctive therapy. Recognizing this, the Committee recommended its inclusion on the Model list.

**Section 10: Medicines affecting the blood**

**Tranexamic acid (Inclusion)**

An application for inclusion of tranexamic acid was prepared by the WHO Collaborating Centre, University of Newcastle, Australia following a proposal from the Cochrane Injuries Group (Dr Ian Roberts, London School of Hygiene and Tropical Medicine).
Expert reviews of the application were prepared by Dr Cranswick, and Dr Cheraghi.

The Committee noted that cardiac surgery is associated with high risks of massive blood loss (156). Massive blood loss is strongly associated with in-hospital mortality (156). Transfusions with RBC’s are costly (157) and have several associated adverse events (158). The blood bank costs are also rising due to the increasing number of safety measures required (159).

The Committee acknowledged that tranexamic acid is effective in reducing peri-operative blood loss in cardiac surgery in adults but the potential benefit in terms of reducing transfusion was not described. Tranexamic acid was found to have no significant difference in effect compared with placebo on myocardial infarction, stroke, deep vein thrombosis, pulmonary embolus, renal failure/dysfunction, or death (160, 161). The Committee also questioned the public health importance of this indication. Additional evidence identified by the Secretariat showed that tranexamic acid may decrease blood loss in orthopedic surgery and partial hepatectomies. However, the currently available literature on the clinical utility of tranexamic acid in orthopedic surgery is not clear.

The Committee concluded that there is not enough evidence of effectiveness in indications that are relevant to public health priorities to support the inclusion of tranexamic acid at this time.

**Section 12: Cardiovascular medicines**

**Section 12.2: Antiarrhythmic medicines**

**Amiodarone (Inclusion)**

Following a request from the Expert Committee in 2007, an application was prepared by the WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health for the inclusion of amiodarone; tablets 100 mg, 200 mg, 400 mg and 50 mg/ml vials and ampoules, for both the acute and chronic treatment of supraventricular and ventricular arrhythmias.

Expert reviews of the application were prepared by: Dr Gregory L. Kearns and Professor Abdol Majid Cheraghi.

The Committee noted that the efficacy and safety data presented in the application were derived from RCTs and systematic reviews and generally supported the view that amiodarone is both effective and safe for the use in arrhythmic disorders, but did not support the use of amiodarone in the routine treatment of chronic heart failure.

The Committee also noted the role of amiodarone in selected acute care settings. Amiodarone is recommended in both the PALS and ACLS guidelines for cardiac arrest with pulseless VT or VF (unresponsive to defibrillation, CPR and vasopressor administration). It is also recommended in the PALS guidelines for SVT (unresponsive to vagal manoeuvres and adenosine).
The Committee noted the recommendation that amiodarone treatment should be initiated by a specialist and baseline investigations performed before treatment begins (chest x-ray, pulmonary, thyroid and liver function tests). Thereafter, longitudinal assessment of thyroid and liver function is required and other specialist investigations may be necessary during the course of treatment. Safe use also requires vigilant assessment of concomitant drug-drug interactions with warfarin and digoxin in particular.

Based on the evidence presented in the application the Committee recommended inclusion of amiodarone on the complementary Model list. In the absence of evidence of effectiveness and safety of the medicine in children, the Committee did not add it to the EMLc but requested further review of the antiarrythmics as used in children.

**Section 12.4: Medicines used in Heart Failure**

**Hydrochlorothiazide (New formulations)**

This application was commissioned by the Secretariat as part of a review of the section of medicines used in heart failure. It was prepared by the NHS Centre for the Evaluation of Effectiveness of Health Care (CeVEAS), Local Health Unit Modena, Italy. Comments on the application were received from MSF.

An expert review of the application was prepared by Mr Andy Gray.

The Committee noted the one Cochrane review (162) (N=202) cited showed that thiazides are useful in the relief of symptoms, reduce episodes of de-compensation, and improve exercise tolerance, but do not affect the outcome of heart failure. It also noted evidence of relative efficacy of thiazides in hypertension when compared to beta-blockers (163).

The Committee noted that although thiazides have various potentially serious side-effects, they are relatively safe at doses below 25 mg/day and that their anti-hypertensive effect has largely been achieved at this dose (164).

The Committee noted that the application did not present any evidence for the safety or efficacy of thiazides in children and therefore was not able to recommend addition to the EMLc but requested a further review of pediatric evidence for hypertension.

The Committee supported the inclusion of the 12.5 mg tablet and the suspension form 50 mg per 5 ml of hydrochlorothiazide to the EML for the treatment of hypertension.

**Quinidine (Deletion)**

An application was prepared by the Public Health and Pharmacology Department, Weill Medical College of Cornell University, New York, USA for the deletion of quinidine 200 mg from the Model List.

Expert reviews of the application were prepared by: Dr Kalle Hoppu and Dr Lennita Wannermacher.
The Committee noted that a recent Cochrane review (165) and a large multicentre randomized controlled trial (166) were cited in the application to support the lack of superior efficacy of quinidine over other antiarrhythmic medicines and strategies in prolonging the life of cardiac patients.

The Committee recognized that quinidine has many serious adverse effects; it is associated with increased morbidity, risk of QT prolongation and induction of fatal arrhythmias in the adult population and interacts with a large number of other drugs with potentially fatal consequences, including anti-infectives and antifungals, which are used extensively in developing countries.

The Committee accepted that the evidence presented could also apply to procainamide, another class IA antiarrhythmic agent currently on the Model List.

The Committee recommended the deletion of quinidine and procainamide from the complementary Model List because of the lack of evidence of superior efficacy or safety when compared to other antiarrhythmic medicines and the availability of effective and safer alternatives on, the Model List.

Section 17: Gastrointestinal medicines

Section 17.1: Antiacids and other antiulcer medicines

Omeprazole (Inclusion)

This application was prepared by Universities Allied for Essential Medicines (UAEM) Weill Cornell Medical College — The Rockefeller University–Sloan-Kettering Cancer Institute Chapter. It proposes the addition of omeprazole as a representative of proton pump inhibitors (PPI’s) in the EML core list. Comments in support were received from Médecins Sans Frontières (MSF), who also request maintenance of antacids in the EML core list.

An expert review of the application was prepared by Professor A. Cheraghali.

The Committee noted the public health need for PPI’s in the effective treatment of H. pylori, prevention of gastric cancer and various other conditions, and that PPI’s are recommended by the American college of Gastroenterology Practice Guidelines for Dyspepsia, and the British NHS guidelines.

The Committee noted the evidence provided in the application (based on the National Institute for Clinical and Public Health Excellence Guidelines) and the additional Cochrane systematic reviews identified by the Secretariat that provide evidence of greater efficacy of PPI’s than other therapies for gastro-oesophageal reflux, dyspepsia, and upper gastrointestinal tract bleeding in control of symptoms and inflammation. The same reviews established the comparable efficacy of other PPI’s with omeprazole.

The Committee noted the safety of profile of omeprazole is acceptable for short term use with case reports of rare toxic hepatitis and acute interstitial nephritis. In the long term, PPI’s interfere with calcium absorption resulting in increased prevalence of hip fractures (167), and
increase susceptibility to gastrointestinal and respiratory infections. The minimum effective dose is recommended for long term use. The Committee accepted that the cost per dose of omeprazole is similar to that of histamine receptor antagonists, making PPI's more cost effective.

The Committee recommended the inclusion of omeprazole as a representative PPI in the core list of the EML. It recommended a review of antacids and H2RA to assess their continued usefulness relative to PPI's in the EML and a review of treatment regimens for *H pylori* infections.

Section 17.5: Medicines used in diarrhoea

**Endar (Inclusion)**

An application was submitted by Dr Mahesh Mokashi, from Mumbai, India for the addition of 'Endar' oral syrup to the Model list for the treatment of diarrhoea and dysentery in children and adults.

Expert reviews of the application were prepared by: Professor Anita Zaidi and Dr Elizabeth Zisovska.

The Committee noted that this application was incomplete, did not contain data on efficacy or safety, or information on the composition of the product. Based on the information given in the application the preparation 'Endar' does not currently fit the criteria to be considered as an essential medicine. The Committee therefore rejected the application for inclusion of 'Endar' syrup on the Model List.

The Committee discussed whether applications submitted with inadequate evidence should be considered. The Committee directed the Secretariat to ensure that all applications meet the following criteria before being included in the Committee agenda: (1) they present scientific evidence on efficacy and safety and (2) the medicine has a product composition defined in a way that is reproducible. The Secretariat should screen applications in consultation with Committee members and the relevant WHO departments, as necessary.

**Oral rehydration salts (Inclusion)**

An application was submitted by Dr Olivier Fontaine, Medical Officer, Department of Newborn and Child Health and Development, WHO for the inclusion of a 200 ml pack size of oral rehydration salts (ORS) for the home treatment of diarrhoea on the Model List.

The Committee noted that the efficacy and safety of oral rehydration salts is well established and that a one litre packet has been included on the Model List since its inception in 1977. The ORS formula listed on the Model List was changed in 2003 to a new reduced osmolality ORS solution, which had been shown to reduce the need for unplanned intravenous infusions in the treatment of acute non-cholera diarrhoea in children.

The Committee noted that the rationale for the inclusion of the new 200 ml packet size for ORS was based on the fact that there is now a need to provide an ORS packet more adapted to the home treatment of diarrhoea; which is mainly diarrhoea without dehydration.
The Committee recommended the inclusion of the 200 ml, 500 ml, 1 L packet size of ORS for the home management of diarrhoea as this should increase the acceptability and availability of ORS solution for home use in many countries.

Section 22: Oxytocics and antioxytocics

Misoprostol (Inclusion)

Applications for the inclusion of misoprostol 100 and 200 micrograms tablets were submitted by Gynuity Health Projects and Venture Strategies for Health, for the prevention of post-partum haemorrhage (PPH); and by Gynuity Health Projects, for the treatment of first trimester incomplete abortion.

Misoprostol is currently included on the EML as:

- a 25-microgram vaginal tablet, for use in induction of labour, on the Complementary List (added in 2005);
- in combination with mifepristone as a 200-microgram tablet, for termination of pregnancy (where legally permitted and culturally acceptable), on the Complementary List (added in 2005).

Expert reviews of the applications were prepared by Dr M. Reidenberg and Dr L. Wannmacher.

The public health relevance of treatments for both indications (PPH and incomplete abortion) has been accepted previously by the Expert Committee and is documented in the applications. It is further supported in the many letters received by the Secretariat in support of the proposals from organizations and individuals. In brief, PPH remains the major cause of maternal death (25% of mortality, World Health Report 2005), and the risk of death from PPH is much higher in developing than in developed countries. In addition, atonic uterus is the main cause of PPH (168). The Committee also noted one letter against the proposals, on the grounds of the potential for use of misoprostol as an abortifacient.

(1) Prevention of post partum haemorrhage

The Committee noted the systematic review of 7 trials (169) comparing 600 micrograms misoprostol with other uterotonics. In the context of active management of labour by a skilled birth attendant, in comparison with oxytocin, misoprostol appears to be less effective and is associated with more adverse effects. The major argument made in the application is that misoprostol should be an option in situations where oxytocin is NOT available. The evidence for this claim is based on three published trials (170, 171, 172). The estimates of efficacy of misoprostol compared with placebo are not consistent across the trials that are in settings mostly likely to be similar to those where it is used; there is a significant risk of increased shivering and fever, and an unresolved concern about increased harm due to increased mortality. Furthermore, the Committee is aware of a completed, but not yet reported, large trial assessing the effect of misoprostol on maternal blood loss and mortality.
(2) Treatment of first trimester incomplete abortion

The application identified 22 relevant studies that directly compare the use of misoprostol with surgery for the treatment of incomplete first trimester abortion. Based on these data, there is no statistically significant difference between surgery and oral misoprostol in terms of uterine clearance up to 14 days after administration. Comparison of adverse effects showed that while misoprostol administration was associated with predictable adverse effects (such as bleeding and pyrexia) due to the pharmacological actions of the medicine, these effects generally did not require further interventions (such as blood transfusion) and were reported as acceptable by the women. The adverse effect profile of misoprostol needs to be compared with the potential risks of surgery in unsafe settings. The application cites one unpublished study to support the proposal that 400 micrograms may be equivalent to 600 micrograms orally, but the data are not provided in detail.

The application presents current prices of misoprostol and a brief summary of some published cost effectiveness data.

With respect to use of misoprostol for the treatment of incomplete abortion, the Committee decided that the evidence showed that misoprostol is as effective as surgery and in some settings may be safer as well as cheaper and therefore recommended inclusion of the 200 micrograms tablet on the complementary list with a note indicating the appropriate use; * for management of incomplete abortion and miscarriage.

For prevention of PPH, the Committee decided that the data presented in the application did not establish sufficient evidence of comparative effectiveness, safety or cost effectiveness and therefore the Committee did not include misoprostol for this indication. The Committee will review this decision after the results of the large trial become available.

Section 24: Psychotherapeutic medicines

Section 24.1: Medicines used in psychotic disorders

**Clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone (inclusion)**

An application was prepared by Dr Dale L. Johnson, President of the World Fellowship for Schizophrenia and Allied Disorders for the inclusion of clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone on the Model List for the treatment of psychotic disorders.

Expert reviews of the application were prepared by: Dr Lisa A. Bero and Dr Kalle Hoppu. Comments were received from Dr John McEwen, Member WHO Expert Advisory Panel on Drug Evaluation, Jean Rigal, Medical Director, MSF, France and Dr Benedetto Saraceno, Director of the Department of Mental Health and Substance Abuse.
The Committee noted that, although the application provided some information on the comparative effectiveness and side-effects of the proposed medications, the information presented was neither comprehensively nor a systematic review of the evidence. A literature search undertaken by one of the expert reviewers revealed that evidence from many relevant Cochrane Reviews (173, 174, 175, 176, 177, 178) and a drug class review on atypical antipsychotic drugs by the Drug Effectiveness Review Project (179), had not been included. It was also noted that the application did not provide a comprehensive review of the comparative benefit-risk profiles for the individual medicines.

Regarding clozapine, the Committee noted that it has an important role in the treatment of schizophrenia in people unresponsive to, or intolerant of other antipsychotics. However, the application presented only a limited number of clinical studies to support the efficacy of clozapine and did not present comprehensive information regarding its unique safety issues. Noting the comments on safety from Dr John McEwen, the Committee requested a specific review of clozapine be commissioned before it is considered for inclusion in the Model List.

Based on the evidence presented in this application, the Committee decided not to include an atypical antipsychotic on the list at this meeting. The Committee agreed that there was a need to review the antipsychotic section and requested that a formal application containing a comprehensive summary of the evidence on the comparative effectiveness and adverse effects of these medicines be commissioned as soon as possible by the Department of Essential Medicines and Policy for review at the next meeting.

Section 24.2: Medicines used in mood disorders

Section 24.2.1: Medicines used in depressive disorders

Fluoxetine, paroxetine and sertraline (Inclusion)

An application was submitted by Dr Dale L. Johnson, President, World Fellowship for Schizophrenia and Allied Disorders for the addition of fluoxetine, paroxetine and sertraline to the Model List for the treatment of depressive disorders.

An expert review of the application was prepared by: Dr Lisa A. Bero. Comments in relation to this application were received from Jean Rigal, Medical Director, MSF, France and Dr Benedetto Saraceno, Director, Department of Mental Health and Substance Abuse, WHO.

The Committee noted that the application did not contain a comprehensive review of all the available literature regarding these selective-serotonin reuptake inhibitors (SSRIs). Evidence from relevant Cochrane reviews (180), as well as a recent drug class review for second generation antidepressants by the Drug Effectiveness Review Project (181) were not cited in the application.

Fluoxetine is already on the Model List for this indication.

The Committee decided that the evidence provided was not sufficient to recommend the addition of paroxetine and sertraline or a square box to fluoxetine.
Section 24.3: Medicines used in generalized anxiety and sleep disorders

The Committee was asked to consider the separation of generalized anxiety disorder and sleep disorder into different sections. The Committee noted that although anxiety and sleep problems may simultaneously be present in the same individual there are specific epidemiological and clinical differences between the two conditions, and in recent years these two conditions have been progressively treated with different pharmacological and non-pharmacological interventions. At the present time there are no medicines for listing under sleep disorders, therefore the Committee recommended that sleep disorders should be deleted from the heading of Section 24.3. A new sub-section specifically for sleep disorders on the Model List was not justified at this time.

Addition of a selective-serotonin reuptake inhibitor (escitalopram, paroxetine and sertraline)

An application was submitted by the Dr Corrado Barbui and Dr Andrea Cipriani, Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Italy for the inclusion of a selective-serotonin reuptake inhibitor (SSRI) for the treatment of adults with generalized anxiety disorder on the Model List. The proposed medicines for inclusion were paroxetine 20 mg, sertraline 50 mg and escitalopram 5 mg. Listing was requested as an individual medicine. The application was commissioned by the Department of Essential Medicines and Pharmaceutical Policies, WHO.

Expert reviews of the application were prepared by: Dr Lisa A. Bero and Dr Kalle Hoppu. Comments in relation to the application were received from Jean Rigal, Medical Director, MSF, France and Dr Benedetto Saraceno, Director, Department of Metal Health and Substance Abuse, WHO.

Evidence from randomized controlled trials supported the use of escitalopram, paroxetine and sertraline compared to placebo, benzodiazepines and older antidepressants for the treatment of generalized anxiety disorder (GAD). However, the Committee noted that there was limited information regarding the public health burden of this condition in low- and middle-income countries and that all of the evidence for efficacy and safety had come from clinical trials undertaken in high-income country healthcare settings. The Committee noted that there was not a substantial body of evidence to establish the superior efficacy and safety of one SSRI over another for the treatment of GAD.

The Committee noted that no formal cost-effectiveness analyses have been conducted so far in individuals with GAD.

Overall the Committee decided that the evidence provided in the application did not support the public health need or comparative effectiveness, safety and cost-effectiveness for the addition of escitalopram, paroxetine or sertraline to the Model List at this time.
Section 24.5: Medicines used in substance dependence programmes

**Nicotine Replacement Therapy (NRT) (Inclusion)**

An application was submitted by Dr Douglas Bettcher, Director of Tobacco Free Initiative for the inclusion of nicotine replacement therapy on the Model List. Listing is requested as an example of a therapeutic group under the heading "nicotine (systemic) for smoking cessation". All available dosage forms were specified in the application.

Expert reviews were prepared by: Dr Edgard José Narváez Delgado and Mrs Jehan Mohammed Ali Al-Fannah.

The largest and most recent SR included in the application was a Cochrane Review, that included 111 randomized and quasi-randomized controlled studies of the effectiveness of NRT among 43,040 men and women and demonstrated that all forms of NRT were effective as part of a strategy to promote smoking cessation in individuals (182). However, there were no data showing that availability of NRT reduces smoking rates in a population.

The Committee noted the risk/benefit profile of NRT was well defined and noted that the potential benefits of smoking cessation outweighed the risks of NRT.

The application provided a review of the cost-effectiveness of NRT in a wide variety of countries and settings and in various smoking cessation programmes. However, no data was presented regarding comparable cost-effectiveness between the different types and formulations of NRT.

The Committee considered the addition of NRT in the context of the Framework Convention on Tobacco Control. The Committee recommended that nicotine patches and gum be added to the Model List because of the public health need, high quality evidence of effectiveness, and acceptable safety and cost effectiveness. Other forms were not recommended for inclusion at this time due to less evidence of comparative safety, effectiveness and cost in diverse populations.

**Section 25: Medicines acting on the respiratory tract**

**Section 25.1: Antiasthmatic and medicines for chronic obstructive pulmonary disease**

**Beclometasone (New formulation)**

An application was received from Professor Nadia Ait Khaled of the International Union against Tuberculosis and Lung disease for the inclusion of beclometasone 100 micrograms for the treatment of asthma and chronic obstructive pulmonary disease.
Expert reviews of the application were prepared by: Mrs Jehan Mohammed Ali Al-Fannah and Dr Rohini Fernandopulle. Comments in support of the application were received from Jean Rigal, MSF International.

The Committee noted that beclometasone dipropionate has been in use for almost 30 years as an inhaled asthma medication and is already listed in the Model list in 50 micrograms and 250 micrograms dosage forms. Its efficacy and safety has long been established. The modification is requested on the basis of changes from CFC to HFA formulations and therefore the change in strength is required.

The Committee recommended the addition of the 100 micrograms beclometasone dosage form to the Model list and the deletion of the 250 microgram strength.

**Cromoglicic acid (Re-instatement)**

An email was received from Mr Alan Edwards of the David Hide Asthma and Allergy Research Centre, Isle of Wight, UK. No formal application was prepared for consideration by the Committee.

Expert reviews of the information provided were prepared by: Dr Myriam Henkens and Dr Gregory Kearns.

The Committee noted that the information provided to support the re-instatement of cromoglicic acid did not include any new studies demonstrating its superior efficacy and safety compared to placebo or comparators for the treatment of asthma.

The Committee noted that the Cochrane Review of inhaled sodium cromoglycate in children was up-dated in 2008 in response to criticism of the methods and conclusions in the original review (183). However, the main findings remained the same: there is still insufficient evidence to be sure about the efficacy of cromoglicic acid over placebo for chronic asthma in children.

Evidence from a new Cochrane Review comparing inhaled corticosteroids versus sodium cromoglycate in children and adults with asthma was published in 2006 (184) was provided to the committee by the Secretariat. This review included 17 trials involving 1279 children and eight trials involving 321 adults with asthma. The review found that ICS were superior to SCG on measures of lung function and asthma control for both adults and children with chronic asthma. No differences in adverse effects between ICS and SCG were found.

The Committee did not recommend the re-instatement of cromoglicic acid in the core list at this time and commented that until there is substantial new supporting evidence of its superior safety and efficacy for the treatment of asthma the re-instatement of cromoglicic acid in the WHO Essential Medicine List is not recommended.
Summary of recommendations

Additions, changes and deletions to the Model List

1. **The Committee made the following changes to the Sections:**

   **Section 6.3 and Section 6.5.2:** The listing of liposomal amphotericin B was modified to specify both the deoxycholate and the liposomal form.

   **Section 6.2.2:** Sulfadiazine was deleted from this section as it is only indicated for the treatment of toxoplasmosis.

   **Section 6.5.4:** Sulfadiazine was added to this section because it is only used for the treatment of toxoplasmosis.

   **Section 18:** Fludrocortisone was added to provide concordance with the EMLc since it was noted by the Committee that it would be essential for the treatment of congenital adrenal hypoplasia and adrenal failure in adults.

   **Section 24.3:** The term "sleep disorders" was deleted from the heading of the section on the basis that there are specific epidemiological and clinical differences between generalized anxiety disorders and sleep disorders. The creation of a new sub-section for sleep disorders was not deemed appropriate at this time as there were no specific medicines for listing.

2. **The Committee recommended the following additions to the Model List:**

   **Section 5:** Parenteral diazepam with a square box was replaced by parenteral lorazepam, 2 mg/ml and 4mg/ml in 1 ml ampoule, with a square box. The rectal solution or gel formulation of diazepam was retained on the Model List.

   **Section 6.2.4:** Addition of rifabutin capsule 150 mg with the note: for use in patients with HIV receiving protease inhibitors. Rifabutin was not added to the EMLc at this meeting because there was a lack of evidence of its efficacy and safety in children.

   **Section 6.3:** Addition of the liposomal formulation of amphotericin B.

   **Section 6.4.2.3:** Addition of atazanavir 100 mg; 150 mg and 300 mg solid oral dosage forms.

   **Section 6.4.2.3:** Addition of heat stable fixed dose combination formulations of lopinavir/ritonavir 100 mg + 25 mg and 200 mg + 50 mg tablets.

   **Section 6.4.2.3:** Addition of heat stable ritonavir 100 mg and 25 mg tablets.

   **Section 6.4.2.3:** Addition of saquinavir 500 mg tablet.

   **Section 6.5.5:** Addition of nifurtimox 120 mg tablet with the note, only to be used in combination with eflornithine for the treatment of *Trypanosoma brucei gambiense* infection.
Section 8.2: Addition of carboplatin as the representative platinum compound, 50 mg/5 ml, 150 mg/15 ml, 450 mg/45 ml and 600 mg/60 ml injection.

Section 8.2: Addition of hydroxycarbamide 200 mg, 250 mg, 300 mg, 400 mg and 500 mg capsules and 1 g tablet.

Section 8.2: Addition of ifosfamide 1 g and 2 g vials of powder for injection.

Section 8.2: Addition of mesna 100 mg/ml injection and 400 mg and 600 mg tablets.

Section 12.2: Addition of amiodarone 50 mg/ml injection and 100 mg, 200 mg and 400 mg tablets to the complementary list.

Section 12.3: Addition of hydrochlorothiazide 12.5 mg tablet and 50 mg/5 ml oral liquid.

Section 17: Addition of omeprazole as a representative proton pump inhibitor, 10 mg, 20 mg and 40 mg oral solid dosage form and 20 mg and 40 mg sachets of powder for oral suspension.

Section 17.2: Addition of ondansetron with a square box, 2 mg/ml injection, 4 mg/5 ml oral liquid and 4 mg, 8 mg and 24 mg solid oral dosage form.

Section 17.2: Addition of dexamethasone 4 mg/ml injection, 0.5 mg/5 ml and 2 mg/5 ml oral liquid and 0.5 mg, 0.75 mg, 1.5 mg, 4 mg oral solid dosage form.

Section 17.5.1: Addition of 200 ml and 500 ml and 1 L packet sizes for oral rehydration therapy.

Section 22.1: Addition of misoprostol 200 microgram tablet to the complementary list with the note that it is for the management of incomplete abortion and miscarriage.

Section 24.5: Addition of nicotine replacement therapy chewing gum 2 mg and 4 mg and transdermal patches 5 mg to 30 mg/16 hours and 7 mg to 21 mg/24 hours NRT.

Section 25.1: Addition of beclomethasone 100 microgram per dose inhalation formulation (aerosol, CFC free form).

3. **The Committee recommended that the following medicines should be deleted from the Model List:**

Section 6.2.4: Deletion of the 60 mg + 30 mg combination of rifampicin + isoniazid and the 60 mg + 30 mg + 150 mg combination of rifampicin + isoniazid + pyrazinamide on the basis that these combinations provide an inefficacious dose for children.

Section 6.4.2: Deletion of the 200 mg and 333 mg tablet formulations of indinavir on the basis that these formulations are not needed as part of a comprehensive antiretroviral treatment programme.
Section 6.4.2: Deletion of all formulations of nelfinavir on the basis of non-availability and reduced need for this medicine as part of a comprehensive antiretroviral treatment programme.

Section 6.4.2: Deletion of the 40 mg tablet formulation of stavudine on the basis of its safety profile and to ensure consistency with WHO guidelines.

Section 6.5.2: Deletion of pentamidine powder for injection 200 mg and 300 mg on the basis that it is no longer recommended for the treatment visceral leishmaniasis in adults and to provide concordance between the EML and EMLc.

Section 8.2: Deletion of cisplatin powder for injection 10 mg and 50 mg in vial as carboplatin is superior.

Section 12.2: Deletion of quinidine 200 mg tablet and procainamide 100 mg/ml injection due to their inferior efficacy and safety compared with other antiarrhythmic medicines.

Section 17.2: Deletion of promethazine on the grounds of its lack of efficacy in post operative nausea and vomiting.

4. The Committee considered proposals for the following medicines but rejected their inclusion in the Model List:

Section 4.2: Pralidoxime injection — rejected on the grounds that the current available evidence from studies in adults did not sufficiently demonstrate its efficacy and safety.

Section 5:
Lamotrigine tablets and chewable dispersible tablets — rejected on the grounds of insufficient evidence of its superior safety, efficacy and cost-effectiveness compared to comparators and the availability of suitable alternative antiepileptics which are already on the Model List.
Midazolam oral liquid — rejected on the grounds of insufficient evidence to show its effectiveness and safety in community settings for seizures and the availability of a suitable alternative already on the Model List.

Section 6.4.2.1: Zidovudine + lamivudine + abacavir fixed-dose combination tablet — rejected on the grounds of a lack of specific evidence of the superior efficacy of this fixed dose combination and where the combination is required in individual cases, it can be achieved with the medicines already listed.

Section 6.4.3: Amantadine and rimantadine tablets, capsules and oral liquid formulations, oseltamivir capsules and oral suspension, zanamivir powder for oral inhalation — rejected on the grounds that the evidence to support the effectiveness of any of the four antivirals for treatment of avian flu is of a very low quality.
Section 7: Sumatriptan 50 mg tablet — rejected on the grounds that the comparative efficacy, safety and cost effectiveness of Sumatriptan versus other triptans and aspirin was not established.

Section 10: Tranexamic acid intravenous infusion — rejected on the grounds that there is not enough evidence of its effectiveness in indications that are relevant to public health priorities at this time.

Section 17: Endar syrup — the application was rejected on the grounds that it was incomplete. It did not include any scientific evidence for the efficacy and safety of the proposed product and did not define the product composition in a way that is reproducible.

Section 22.1: Misoprostol 200 micrograms tablet, for the prevention of post-partum haemorrhage — the application was rejected on the grounds that the evidence available to the Committee at the present time did not establish the comparative effectiveness and safety in the proposed context and setting for use of the product.

Section 24.1: Clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone — rejected on the grounds that the application did not provide sufficient information regarding the comparative effectiveness and safety of the proposed medicines. Committee requested a formal review of this section for consideration at the next meeting.

Section 24.2.1: Paroxetine and sertraline — rejected on the grounds of insufficient evidence of their comparative effectiveness, safety and cost-effectiveness at this time.

Section 24.3: Escitalopram 5 mg tablet, paroxetine 20 mg tablet, sertraline 50 mg tablet — rejected on the grounds that the evidence did not support the public health need or comparative effectiveness, safety and cost-effectiveness for their addition at this time.

Section 25: Cromoglicic acid — re-instatement was rejected on the grounds that there was no new supporting evidence to show its superior safety and efficacy for the treatment of asthma at this time.

Additions, changes and deletions to the EMLc

1. The Committee made the following changes to the Sections:

Section 6.2: The age restriction was removed from procaine benzylpenicillin on the basis of potential mortality benefits in neonates with severe sepsis. However, the note was amended to indicate restricted use: not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.

Section 6.3 and Section 6.5.2: The listing of liposomal amphoteracin B was modified to specify both the deoxycholate and the liposomal form.

2. The Committee recommended the following additions to the EMLc:

Section 6.3 and Section 6.5.2: Addition of the liposomal formulation of amphotericin B.
Section 6.5.3.1: Addition of artemeter + lumefantrine 20 mg + 120 mg dispersible tablet.

Section 12.4: Addition of enalapril as the indicative angiotensin-converting enzyme inhibitor, 2.5 mg and 5 mg tablets.

Section 17.2: Addition of ondansetron with a square box, 2 mg/ml injection, 4 mg/5 ml oral liquid and 4 mg and 8 mg solid oral dosage form.

3. The Committee recommended that the following listings for medicines be amended to correct dosage strength and form:

Section 25.1: Strength of budesonide listing was corrected to, 100 micrograms per dose and 200 micrograms per dose inhalation (aerosol).

4. The Committee considered proposals for the following medicines but rejected their inclusion in the Model List for Children:

Section 12.4: Carvedilol tablets — rejected on the grounds that there was not enough evidence of its comparative effectiveness and safety to justify inclusion in the complementary list of the EMLc.
### Appendix 1: Proposed lists of priority essential medicines for HIV

#### 1. UNITAID secretariat /WHO proposal

<table>
<thead>
<tr>
<th>Adults: missing essential medicines Medicine/form</th>
<th>Rationale from current treatment guidelines or EML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stand-alone thermostable formulations of ritonavir or in combination with other PIs e.g. atazanavir/ritonavir (ATV/r) indinavir/ritonavir (IDV/r) saquinavir/ritonavir (SQV/r) fosamprenavir/ritonavir (FPV/r)</td>
<td>Thermostability critical for use in resource limited settings PIs 'boosted'; with ritonavir are recommended for use in second line treatment regimens.</td>
</tr>
</tbody>
</table>
| Triple drug 1^st^ line combinations:  
  Tenofovir(TDF) based triple combinations plus efavirenz (EFV) or nevirapine (NVP) plus lamivudine (3TC) or emtricitabine (FTC) e.g. TDF/FTC/NVP TDF/3TC/NVP TDF/FTC/EFV TDF/3TC/EFV  
  Zidovudine(AZT) based triple combinations plus lamivudine or emtricitabine plus abacavir (ABC) or tenofovir e.g. AZT/3TC/ABC AZT/FTC/ABC AZT/3TC/TDF AZT/FTC/TDF | These are all recommended combination regimens for first line ART; all are on the EML as individual components, 2 drugs as fixed dose combinations (FDCs) also exist but with limited availability |
| Alternative dual combinations based on lamivudine or emtricitabine plus tenofovir  
  TDF/FTC  
  TDF/3TC | Possible combinations based on current EML listing; limited availability at present. |
| Possible valuable second line triple combinations based on lamivudine or emtricitabine plus tenofovir and a once daily boosted PI (e.g. ATV/r, LPVr) LPV/r/TDF 3TC LPV/r/TDF/FTC ATV/r/TDF/FTC ATV/r/TDF /3TC | Components are all on EML and or treatment guidelines; second line regimens need further evaluation ideally as once daily FDCs. |
| Possible valuable second line dual and triple combinations:  
  Alternative dual combinations based on lamivudine or emtricitabine plus didanosine enteric coated (ddI) ddI/3TC ddI/FTC  
  Triple combinations based on lamivudine or emtricitabine plus didanosine EC and a once daily |  |
### Adults: missing essential medicines

<table>
<thead>
<tr>
<th>Medicine/form</th>
<th>Rationale from current treatment guidelines or EML</th>
</tr>
</thead>
</table>
| boosted PI (e.g. ATV/r, LPVr)  
LPVr/ddI/3TC  
LPVr/ddI/FTC  
ATV/r/ddI/FTC  
ATV/r/ddI/3TC | |

### Table 2. Priority Paediatric products

<table>
<thead>
<tr>
<th>Priority</th>
<th>Product</th>
<th>Recommended Ideal Dosing strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended priority Antiretroviral products for infant MTCT prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent</td>
<td>Zidovudine</td>
<td>12 mg sachet granules</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>6 mg sachet granules</td>
</tr>
<tr>
<td><strong>Recommended priority antiretroviral products required for treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent</td>
<td>Zidovudine/Lamivudine/Nevirapine</td>
<td>60/30/50 mg tablet*</td>
</tr>
<tr>
<td></td>
<td>Zidovudine/Lamivudine</td>
<td>60/30 mg tablet</td>
</tr>
<tr>
<td></td>
<td>Stavudine/Lamivudine</td>
<td>6/30 mg tablet*</td>
</tr>
<tr>
<td></td>
<td>Stavudine/Lamivudine/Nevirapine</td>
<td>6/30/50 mg tablet*</td>
</tr>
<tr>
<td></td>
<td>Abacavir/Zidovudine/Nevirapine</td>
<td>60/60/50 mg tablet*</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
<td>50 mg tablet*</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir</td>
<td>100/25mg tablet*</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
<td>60 mg tablet</td>
</tr>
<tr>
<td>High</td>
<td>Efavirenz</td>
<td>100 mg tablet</td>
</tr>
<tr>
<td></td>
<td>Abacavir/Lamivudine</td>
<td>60/30 mg tablet</td>
</tr>
<tr>
<td></td>
<td>Zidovudine</td>
<td>60 mg tablet</td>
</tr>
<tr>
<td></td>
<td>Zidovudine/Lamivudine/Abacavir</td>
<td>60/30/60mg tablet</td>
</tr>
<tr>
<td></td>
<td>Stavudine</td>
<td>6 mg tablet*</td>
</tr>
<tr>
<td>Important</td>
<td>Lamivudine</td>
<td>30 mg tablet</td>
</tr>
<tr>
<td></td>
<td>Efavirenz/Emtricitabine</td>
<td>100/35mg tablet</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine</td>
<td>35 mg tablet</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>25 mg tablet</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Not examined</td>
</tr>
<tr>
<td></td>
<td>Atazanavir</td>
<td>Not examined</td>
</tr>
</tbody>
</table>
## 2. MSF proposals for additional adult missing essential medicines for UNITAID patent pool initiative as of 23.03.09

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reasons for inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Protease Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>A new class. Indicated for treatment experienced, multi class resistant patients. Can be used in treatment naïve patients but not in international guidelines for this indication. Very well tolerated. An important advancement in HIV-1 treatment option.</td>
</tr>
<tr>
<td>Integrase Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Maravirocin</td>
<td>A new class. Indicated for treatment experienced/ multi-resistant patients with only CCR5 tropism. HIV-1 subtype C virus seems to carry majority of CCR5 receptors. Use of maravirocin in African subtypes limited.</td>
</tr>
<tr>
<td>CCR5 Receptor Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>Active against mutant NNRTI resistant HIV strains.</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Undergoing Phase III study. Not yet commercialized but promising drug as it is potent, and can be used once daily (with low dose (25mg,))</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Undergoing Phase II-III with a booster GS-9350. Potential for being co-formulated.</td>
</tr>
<tr>
<td>Integrase inhibitor</td>
<td></td>
</tr>
<tr>
<td><strong>Booster</strong></td>
<td></td>
</tr>
<tr>
<td>Ritonavir (r) heatstable</td>
<td>The only booster commercially available with other PIs</td>
</tr>
<tr>
<td>GS-9350</td>
<td>Non ARV booster. Entering phase II-III studies. Developed for combination with elvitegravir, and potentially with elvitegravir, TDF and FTC.</td>
</tr>
<tr>
<td>CYP 3A inhibitor,</td>
<td></td>
</tr>
<tr>
<td>SPI-452</td>
<td>Non ARV booster. Only preclinical study done.</td>
</tr>
<tr>
<td>CYP 3A inhibitor,</td>
<td></td>
</tr>
<tr>
<td><strong>Fixed dose combinations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>1. Heat stable boosted PI (combined with ritonavir)</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir /ritonavir</td>
<td>Validated for first line and treatment experienced patients. Advantage of FDC is once daily dosing.</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td>Alternative PI for treatment naïve or experienced patients. Can be used once or twice daily.</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>Potent PI with main indication for salvage or second line regimens. Can be used once or twice daily.</td>
</tr>
<tr>
<td><strong>2. Heat stable PI PLUS NRTIS for second line</strong></td>
<td></td>
</tr>
<tr>
<td>LPV/r/TDF/ 3TC</td>
<td>Component of second line regimens in current WHO guidelines and expert meeting on second lines (2008). LPV/r can be given once daily in PI naïve patients. All didanosine (ddl) containing combinations are suggested.</td>
</tr>
<tr>
<td>ATV/r/TDF/ 3TC</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Reasons for inclusion</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>LPV/r /ABC + ddI</td>
<td></td>
</tr>
<tr>
<td>LPV/r /3TC + ddI</td>
<td></td>
</tr>
<tr>
<td>ATV/r /3TC + ddI</td>
<td>Co-blisters are needed at the moment as it can only be</td>
</tr>
<tr>
<td></td>
<td>manufactured in buffered tablets or enteric coating.</td>
</tr>
<tr>
<td>ATV/r /3TC /ABC</td>
<td></td>
</tr>
</tbody>
</table>

3. **FDC for first line combinations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reasons for inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF /3TC + NVP (co-</td>
<td>Currently recommended first line. Interesting combination</td>
</tr>
<tr>
<td>blister)</td>
<td>but NVP is usually given twice daily at least in the first</td>
</tr>
<tr>
<td></td>
<td>3 to 6 months.</td>
</tr>
<tr>
<td>TDF/3TC/EFV</td>
<td>Exists in co-formulation and widely used first line</td>
</tr>
<tr>
<td></td>
<td>internationally. More sources needed (only orginators</td>
</tr>
<tr>
<td></td>
<td>available now)</td>
</tr>
</tbody>
</table>

**MSF proposal for additional Paediatric essential medicines for UNITAID patent pool initiative as of 23.03.09**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason for inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td>Potent protease inhibitor(PI)</td>
</tr>
<tr>
<td>Ritonavir heatstable</td>
<td>For boosting with other PIs.</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Alternative PI</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Alternative PI</td>
</tr>
</tbody>
</table>

**MSF proposal for urgent studies in children**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason for urgent need of studies in children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine</td>
<td>Not yet tested in children</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Not yet tested in children</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Accelerate testing</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Accelerate testing in children below 3 years</td>
</tr>
<tr>
<td></td>
<td>old</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Accelerate testing in children below 6 years</td>
</tr>
<tr>
<td></td>
<td>old</td>
</tr>
</tbody>
</table>
Appendix 2: Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children

WHO Headquarters, Geneva, Switzerland, 15-16 December 2008

This publication contains the Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children and does not necessarily represent the decisions or policies of the World Health Organization.
Executive summary

In December 2008, a group of pediatricians, pharmacists, clinical pharmacologists, and representatives of the EMEA, IFPMA, MMV, NIH, UNICEF, and the Bill and Melinda Gates Foundation attended a meeting hosted by the WHO to discuss the preferred dosage form of medicines for children. The meeting considered the terms of reference in relation to dosage forms of medicines for children provided to the Expert Subcommittee on Selection and Use of Essential Medicines by the Executive Board in May 2007. A review of published information on different dosage forms of medicine for children was provided to the meeting participants, together with a review of end-user needs. The influence of socio-cultural issues on the acceptability of dosage forms of medicines used for children was also considered in the discussion.

As a result of this consultation, the group identified the dosage forms of medicines most suitable for children with particular attention to conditions prevailing in the developing countries, and flagged future areas of research required in this area. This report summarizes the existing evidence, provides an overview of the meetings outcomes and details the suggested recommendations. It will be reviewed by the Expert Committee on Selection and Use of Essential Medicines at its next meeting in March 2009, in the context of the report from the Subcommittee on Essential Medicines for Children.

Declaration of interests

Expert participants in the Informal Expert Meeting on Dosage Forms for Children meeting reported the following relevant interests (in accordance with WHO procedures, for the period of the last 3 years):

- Professor Jorg Breitkreutz reported receiving research support from DSM, Austria, Medice Germany, Gen-Plus Germany, Bayer Schering Germany, and holding shares in Ethicare GmbH, Germany.
- Professor Kalle Hoppu reported receiving lecture fees from Leiras Ltd, Finland, Oy Swedish Orphan Ab Finland, Norit Pharmaceuticals, the Netherlands and one-time consultation fees from Lundbeck A7S, Denmark.
- Dr Stuart MacLeod reported receiving one-time consulting fees from Eli Lilly, and that the Research Unit of which he is Executive Director receives grants from several pharmaceutical and biotechnology companies, but that he is not a principal investigator on any of these projects.
- Professor Tony Nunn reported that his research unit receives grants from the UK National Institute for Health Research.
- Dr Stephen Spielberg reported being the Principal Investigator of IPI.

Professor Rohini Fernandopulle, Dr George Giacoia, Professor Henning Kristensen, Dr Jane Robertson and Dr Peter York reported no interests. Dr Herrad-Odilia Krenkel and Dr Klaus Rose are employees of commercial organizations.
Introduction

The global mortality rate in children under five years remains a significant and inequitable problem, particularly within the disease groups of malaria, HIV, tuberculosis, pneumonia, diarrhea and neonatal infections. Medicines for children have long been a neglected area. The lack of appropriate pediatric dosage forms, scarcity of research within the pediatric area, and lack of details of the dose (and age-related dose) of paediatric medicines (an important pre-requisite in the design of any paediatric medicine) results in children being frequently prescribed medicines that are off-label, unlicensed, or that have been manipulated prior to administration. As a direct consequence, children and their caregivers are routinely do not have access to safe, effective and appropriate treatment, an effect which significantly contributes to the high mortality and morbidity rates within this age group.

At its meeting in September 2008, the Expert Subcommittee on Selection and Use of Essential Medicines for Children noted that further work still needed to be completed to fully address two of the terms of reference of the Subcommittee:

- to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in developing countries;
- to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups.

The aim of this meeting on dosage forms of medicines for children was, therefore, to bring together pediatricians, pharmacists, clinical pharmacologists and formulation experts to review the existing evidence in the field on appropriate pediatric formulations, and to identify future research needed to improve the development of preferred dosage forms for children.

Meeting background

Meeting objectives

1. To review the published evidence on what dosage forms of medicines have been developed and administered to children.
2. Determine which existing or novel dosage forms and delivery methods are appropriate for children, considering the feasibility of manufacture.
3. Recommend a preferred dosage form(s) of medicine for children, spanning across different geographical and cultural settings.
4. Identify research needs required to define the preferred dosage form of medicines for children.
Preparatory work

1. A comprehensive review of the published literature, describing current technologies and dosage forms of medicines for children was carried out by Professor Peter York and Dr Amir Amani prior to the meeting.

2. A survey of end-user needs for preferred pediatric dosage forms was carried out by Ms Atieno Ojoo, and a draft document of these findings was prepared by Ms Atieno Ojoo and Dr Kalle Hoppu.

3. A literature review on socio-cultural issues that influence the acceptability of pediatric dosage forms was carried out by Drs Sienna Craig, Lisa Adams and Stephen Spielberg.

These reviews served as the basis for the meeting participants to propose recommendations for the Expert Committee to consider. All literature reviews, background documents and meeting presentations are available upon request.

Summary of meeting discussion

The meeting was opened by Dr Hans Hogerzeil (Director, Department of Essential Medicines and Pharmaceutical Policies). Dr Hogerzeil highlighted the discrepancy in the availability of suitable medicines for children when compared to those available for adults, and emphasized the significant impact in reduction of childhood mortality and morbidity that could be achieved through improvement in the global access of suitable medicines for children.

Professor Peter York presented his review of the currently available dosage forms of medicines for children, and innovations in drug delivery design for children. He outlined the requirements for pediatric medicines, commented on the suitability of available dosage forms for pediatric medicines, and identified recent innovations in dosage form designs and technologies.

Mr David Ubben provided an overview of the work of the Medicines for Malaria Venture, and commented specifically on the progress and challenges made with the development of three new pediatric antimalarial combinations.

Dr Atienno Ojoo presented a survey of the end user requirements for preferred pediatric formulations. She emphasized the importance of taking into account specific end-users needs including children, parents/caregivers, nurses, pharmacists, prescribing physicians and other health care workers.

Dr Stephen Spielberg provided an overview of the important socio-cultural issues to consider in improving pediatric dosage forms. He suggested that aspects such as acceptability, palatability, tolerance and compliance may vary widely between different cultural settings, and could be significantly influenced by socio-cultural issues.
Professor Rohini Fernandopulle presented a survey of care givers in Sri Lanka, outlining some of the problems faced when using currently available dosage forms of anticonvulsants to treat epilepsy in children.

**Summary of evidence**

**Currently available and innovative paediatric dosage forms — Peter York and Amir Amani**

Eight hundred (English language) citations were retrieved, containing references to current activity and innovations in drug delivery system design for children. Identified routes of administration were oral (liquid and solid dosage forms), topical, parenteral, inhalational and nasal, rectal and ocular routes. No clear trends were identified, and most clinical papers did not report full details of new dosage forms used in studies. There was general acceptance of the benefits of solid dosage forms over liquid dosage forms for stability, dosing and administration issues. Only a limited number of reports attempted to bridge the gap between 'top down' and 'bottom up' approaches, and/or include manufacturing and regulatory aspects of paediatric dosage forms. The need for a multidisciplinary and 'holistic' approach to paediatric medicines was highlighted and the potential of a 'platform' solid dosage form (e.g. granules or pellets) as a preliminary form providing flexibility for further processing into a range of alternative paediatric drug delivery systems was presented.

The meeting noted that despite several studies reporting small children as unable to swallow granules or mini-tablets, there was a lack of evidence for a specific age at which solid dosage forms are clearly acceptable from clinical and safety perspectives, and further research was needed on this topic.

The meeting agreed that a restricted focus on 'innovative' medicines would be counter productive to the development of paediatric dosage forms, and that it was important to consider the modification of standard technologies in the development of preferred paediatric dosage forms.

The meeting suggested that focusing on the development of suitable dosage forms used to treat diseases of high burden in childhood (i.e. diarrhoea, pneumonia, neonatal sepsis, prematurity, HIV, TB and malaria), would achieve the highest impact for reduction in childhood morbidity and mortality. An additional consideration was the discussion of potential differences in dosage forms for treatment required for acute versus chronic diseases. It was noted that precision of dosing appeared to be less important in the treatment of many public health priorities, where the majority of medicines currently used have a wide therapeutic index and the main risk may be underdosing, with resultant inefficacy, rather than excessive dosing with associated risks of toxicity.

It was also emphasized that for children of different age groups, dose combinations would require varying percentages of drug composition depending on each drug's respective absorption, distribution, metabolism and excretion.

The meeting acknowledged that treatment failure as a measure of outcome was important, and that cost was relevant in the development of preferred paediatric dosage forms.
Desirable attributes of a paediatric dosage form

Several requirements were identified as key in the identification of a preferred paediatric dosage forms. These included:

- Minimal administration frequency
- Minimal impact on life style
- Minimum, non-toxic excipients
- Convenient, easy, reliable administration
  - Palatable
  - Requiring minimal manipulation by health professionals or carers prior to use (i.e. flexibility/adaptability of the medicine to account for developmental and size differences, with the ability to reliably divide the unit dose.)
- Transportable and low bulk/weight
- Easily produced, stable in a variety of climates
- Affordable
- Commercially viable

End-user needs — Atieno Ojoo and Kalle Hoppu
Rohini Fernandopulle

An email survey of 38 respondents from 27 countries (including both high, low and middle income countries) was carried out in order to determine end-user specifications for preferred paediatric dosage forms. Responses were found to be similar across all geographic regions, and in all high, low and middle income countries. Problems identified included supply challenges, health worker challenges, quality issues, storage problems, and specific end-user issues such as palatability, lack of information, care-giver fatigue, pill burden and off-label medicine use. Other general issues included problems with access to clean water and lack of training of dispensing staff, issues which are particular problems for resource poor countries.

A survey of care givers in Sri Lanka was also presented, outlining some of the problems faced when using currently available dosage forms of anticonvulsants to treat epilepsy in children.

On the basis of these findings, it was suggested that interventions should be targeted at the levels of research and development, policy makers, manufacturers and procurement and logistics.

Socio-cultural aspects — Sienna Craig and Stephen Spielberg

A draft literature review (Sienna Craig et al.) on the sociocultural aspects of paediatric dosage forms highlighted the importance of cultural setting in suitability of dosage forms, with cultural differences noted in the understanding and expectations of treatment, duration of treatment, palatability, and acceptability of medicines.
Although the meeting acknowledged that cultural setting was important, it was noted that there was insufficient evidence to demonstrate a true variation in cultural acceptability. The possibility of producing a product that would be acceptable across multiple cultures through a platform technology that could be ‘reformatted’ to meet cultural norms, was therefore considered. Platform technologies are technologies that can be used to facilitate a broad range of application based activities. i.e. one formulation technology can be used for several active compounds.

**Proposed recommendations**

1. In general, the dosage forms of medicines that are likely to prove most ‘suitable’ particularly for developing countries are flexible solid dosage forms, such as tablets that are oro-dispersible and or that can be used for preparation of oral liquids (for example suspension or solution). These dosage forms could be used for many of the medicines that are necessary to treat the diseases that are the major causes of mortality and morbidity in under 5s (Lower respiratory tract infection, malaria, diarrheal diseases).

   Provided the product can be dispersed in breast milk from the mother, it could potentially be used in very young children (0-6 months). This type of product is feasible to manufacture in facilities that have conventional tableting facilities, but requires excipients that ensure stability and palatability. Examples of existing dispersible tablet products suggest that they can be more affordable than standard liquid dosage forms.

   It is necessary to identify appropriate product strengths and ratios of actives (based on physiological development expressed as age or weight bands and with simple dosing regimens) for each medicine, as well ensuring package sizes that allow optimal use under public health programmatic conditions.

   This type of product may not be suitable for medicines requiring precise dose titration, such as some anticonvulsants, or molecules that are Biopharmaceutics Classification System (BCS) classes 2 and 4. Drug substances classified as BCS Class 2, are those with high permeability and low solubility, drug substances classified as BCS Class 4 have low permeability and low solubility.¹

2. For severe disease conditions (e.g. neonatal sepsis), injections are the best existing option, but developments should include modified vial sizes or strengths to ensure

1. When an API shows a dose: solubility ratio of 250 ml or lower at 37 °C over a pH range of 1.2–6.8, it can be classified as “highly soluble”. When an API is absorbed to an extent of 85% or more, it is considered to be “highly permeable”.

**References**


suitability for all age groups (especially neonates) and packaging options that allow easy use. There needs to be development of injections and infusions that minimize risk of electrolyte overload. New developments in injection technology should be assessed, especially those that can be used in community or primary care settings.

3. For oral medicines requiring precise dose measurement or titration, the most 'suitable' dosage form should be based on use of a solid platform technology (multi particulate solid, including those that could be dispersed to form a liquid dose), rather than oral liquids. This can allow production of 'tailored' doses and strengths as well as preparation as a range of dosage forms such as tablets or capsules. Examples of current forms are mini-tablets and spherical granules (pellets). In terms of feasibility for the manufacturer, these dosage forms can be manufactured from standard excipients including those that are pre-mixed and suitable for a range of actives, and they have potential flexibility for constructing appropriate FDCs.

4. Techniques for 'difficult molecules' (defined using BCS classes) need to be developed/or evaluated, including manipulation (e.g. spray drying, micronization) prior to use with some platform that may produce suitable dosage forms for children.

5. As an alternative to injections in severely ill children or children unable to swallow, the use of rectal preparations for indications of severe malaria, pain and infection may be appropriate. Rectal preparations of analgesics exist but would need to be assessed for suitability for hot climates. There may be potential value in the development of some antibiotics as rectal preparations but not all would be suitable for this approach because of erratic bioavailability and/or cultural barriers.

6. Patch/transdermal drug delivery technology may be of use for medicines requiring constant plasma concentrations, but needs to be evaluated further. On the one hand, the technology is likely to remain comparatively expensive, and may not be appropriate for all climates, but there may be unpublished data available to facilitate their assessment and a full evaluation is warranted. It is important that patches are not cut, as this may alter release characteristics.

7. Inhalational administration of substances is necessary for treatment of asthma and chronic lung disease, and has been evaluated for delivery of other molecules. There is a need for development of affordable and standardized devices for administration, although it is recognized that the technology may be complex.

8. Medicines for respiratory distress in neonates are available but in the case of surfactant are expensive and difficult to deliver. New approaches to delivering this product are needed.

9. Other less invasive methods of delivering drugs to children have been developed (buccal, nasal etc) but at present the technologies are either not generally affordable or available. Further study is warranted.

10. Researchers should ensure that full details on any new dosage forms used in paediatric clinical studies, are included in publications. A centralized accessible data base of published work on paediatric medicines, and where high-quality medicines in appropriate dosage forms are available, should be established.
Research needs

The following research needs were identified:

1. What particle sizes can be comfortably and safely ingested at different ages and developmental stages in children? [This aspect should be looked at from the perspective of both acute and chronic diseases.]

2. To optimize the acceptability of dosage forms, what standards should be set for 'granularity' (i.e. the size of the components of the medicine) and 'texture' or mouth feel (i.e. the 'feeling' of a liquid, semi-solid or suspension in the mouth), taste and smell, at different ages and developmental stages.
   - For the products commonly used for priority diseases?
   - For other products (by BCS class)?

3. What are appropriate standards for palatability testing (where needed) in children, and how should it be done?

4. What evidence exists to define optimal frequency of dosing (and pill burden) in terms of impact on adherence and clinical outcomes? [Consider treatment in diseases requiring both chronic and acute care.]

5. What are true component costs of different dosage forms of medicines for children?

6. What might be effective strategies for implementing programs that introduce dispersible tablet/other new forms? E.g. zinc, cotrimoxazole experiences – including the importance of policy advocacy.

7. What can be done to standardize and inform on methods for the manipulation of authorized dosage forms (extemporaneous preparation versus manipulation prior to administration) in children?

8. What is the best method of providing information for health workers and carers, related to the optimal administration of medicines to children? E.g. pictograms, auditory messages.

9. What can be done to develop a micro-coating that is absorbable, dissolvable, and immune to degradation by chewing, and environmental or delivery-vehicle temperature changes?

Next steps and outstanding issues

The recommendations from this technical meeting will be published on the Expert Committee meeting website, reviewed by representatives from industry, academia and end-users in the public and private sector, and discussed at the next meeting of the Committee on Essential Medicines in March 2009. The literature reviews will be further developed and submitted for publication. Additional information will be sought from other potential resources such as the food industry and the 'over the counter medicine' industry, who may be able to provide relevant input on aspects in the development of pediatric dosage forms such as palatability and patient preference.
Promotion of the need for the preferred dosage forms is required. Pharmaceutical companies interested in the manufacture of these dosage forms need to be identified. Health care workers and carers of children need to expect ‘preferred dosage forms’.

In order to address the urgent and outstanding research needs identified above, strengthening the quality and quantity of pediatric clinical trials research is essential. A Clinical Trial Registry Platform has been created in order to improve the profile, quality and monitoring of paediatric clinical trials. In addition to this, the panel emphasizes the need for continued advocacy in the area of children’s medicines, particularly with the creation of market demand through prescribers and patients.

It is acknowledged that recommendations currently being presented are not fixed, and that depending on the degree and speed of further technological development, they will probably require revision in subsequent years.
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ANNEX 1: 16th Essential Medicines List
ANNEX 2: Second EMLc
ANNEX 3: The Anatomical Therapeutic Chemical (ATC) classification system

* Medicine or item name differs slightly from the name used.
ANNEX 4: Alphabetical list of essential medicines (with ATC classification code numbers)

* Medicine or item name differs slightly from the name used.
PART TWO
Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines
Second Meeting of the Subcommittee of the 
Expert Committee on the Selection and Use of 
Essential Medicines 

Geneva 29 September to 3 October 2008

Mrs Jehan Mohammed Ali Al-Fannah, Department of Pharmacy, Royal Hospital, Muscat, Sultanate of Oman (Vice-Chair)

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Dr Sarah Hanieh, Research Officer, Medicines Access and Rational Use, Department of Essential Medicines and Pharmaceutical Policies, WHO, Geneva, Switzerland
1. Introduction

The Second Meeting of the WHO Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 29 September to 3 October 2008. The meeting was opened on behalf of the Director-General by Dr Hans Hogerzeil, Director of the Department of Essential Medicines and Pharmaceutical Policies, who noted that this was the second meeting of the Subcommittee, following its original approval by the Executive Board in May 2007 (EB121.R2). He outlined the procedures of the meeting to participants, noting that the Subcommittee is not a representative one and that all members participate in their personal capacity and are not allowed to take instructions from any government or other authority.

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 for Children (EMLc). For Subcommittee members it provided an opportunity to receive, at first hand, additional information and opinion on matters under consideration. The discussions and considerations of the open session are reflected in the report of the meeting.

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 the report but remain available on the WHO web site (http://www.who.int/selection_medicines/committees/subcommittee/2/en/index.html).

2. Open session

The open session was opened by Dr Hans Hogerzeil. He welcomed external participants and noted that all comments made during the session would be noted and taken into consideration by the Expert Subcommittee when formulating their recommendations.

The Secretariat provided an update on work undertaken since the first meeting of the Subcommittee in 2007, including progress made in relation to the World Health Assembly Resolution on Better Medicines for Children. This update included highlighting the global burden of disease mortality in children younger than five years of age, and some of the challenges of ensuring equitable access to essential medicines for children in different countries (for example, limits on logistical capacity in isolated island countries). Progress with work on the Resolution was also described, including the assessment of availability of medicines for children in several countries, the revision of national medicines lists to include medicines for children, and the launch of an advocacy campaign, “Make Medicines Child Size” that aims to promote the development of appropriate high-quality essential medicines for children.

Participant statements were received from:

— Dr Kate Armstrong, President of CLAN (Congenital Adrenal Hyperplasia: Caring and Living as Neighbours);
— Dr Myriam Henkens, International Medical Coordinator of Médecins Sans Frontières (MSF);
— The representative for the Permanent Mission of Canada;
— Mrs Hanne Bak Pederson, UNICEF;
— Dr Rajiv Bahl, WHO Department of Child and Adolescent Health and Development.

Comments were received from UNICEF, reiterating the importance of the EMLc, and from the Child and Adolescent Health and Development Department of WHO, which welcomed the opportunity to be involved in the Subcommittee meeting to offer its perspective on several of the applications.

In their absence, the Secretariat read statements from Dr Armstrong and Dr Henkens. Dr Armstrong wished to emphasize the essential and global requirement for hydrocortisone and fludrocortisone as life-saving drugs in the management of congenital adrenal hyperplasia and adrenal insufficiency, and urged their inclusion on the EMLc. Médecins Sans Frontières sent a number of comments outlining its support for the inclusion of liposomal amphotericin B, doxycycline, oral salbutamol and quinolones on the Core List, but opposing the addition of lindane. The representative of the Permanent Mission of Canada posed a question to the Subcommittee regarding the proposal for the deletion of vitamin A 50 000 IU capsule.

3. Review of terms of reference

The Subcommittee reviewed the terms of reference provided to it by the Executive Board, which are reproduced below. Discussion of the terms of reference is included in this section of the report; amendments to the Model List of Essential Medicines for Children are discussed in Section 4.

The Executive Board:

1. DECIDES to establish as from June 2007 a temporary Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines, of no more than 15 members, with the following terms of reference:

   • to prepare a list of medicines for children, based on their clinical needs and the burden of disease, that the WHO Expert Committee on the Selection and Use of Essential Medicines can use to revise and regularly update the WHO Model List of Essential Medicines to include missing essential medicines for children;
   • to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in the developing countries;
   • to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups;
• to identify the clinical-research gaps regarding safety and efficacy of essential medicines for children in order to improve suboptimal prescribing and dosing, and to facilitate regulatory approval of paediatric formulations;

• to report to the Expert Committee on the Selection and Use of Essential Medicines in 2009.

2. FURTHER DECIDES that the temporary Subcommittee shall terminate in 2009, after its report to the Expert Committee on the Selection and Use of Essential Medicines.

The Subcommittee evaluated its progress based upon the terms of reference given to it by the Executive Board. A summary of progress for each of the terms of reference is provided as follows:

Term of reference 1 – prepare a list of medicines for children, based on their clinical needs and the burden of disease, that the WHO Expert Committee on the Selection and Use of Essential Medicines can use to revise and regularly update the WHO Model List of Essential Medicines to include missing essential medicines for children

Through review and deliberations, the Subcommittee substantially increased and refined the information contained in the EMLc, which had been presented and approved in 2007. The proposed second WHO Model List of Essential Medicines for Children is provided as Annex 2 to this report, and will be submitted to the Expert Committee to review and approve at its next meeting. Further discussion of this List can be found below, under term of reference 5.

In spite of these accomplishments, work remains incomplete, largely due to the volume of information necessary to construct an EMLc that will meet the needs of the world’s children. During its deliberations, the Subcommittee worked diligently to identify gaps while dealing with a wide range of information (relating to clinical pharmacology and therapeutics, clinical toxicology and pharmacovigilance) associated with medicine products, their availability in formulations suitable for children in both developed and developing nations, and their suitability for use in children. The decisions reached and recommendations made by the Subcommittee were largely driven by considerations of therapeutic decision-making as opposed to generating lists of specific products. Decisions were based on review of available accumulated evidence whenever possible as opposed to simply reflecting current practice. The Subcommittee recognizes that when data are not available from paediatric clinical trials, there is still an imperative to make decisions based on the available information as it is unethical to deprive children of access to necessary treatment.

Term of reference 2 – to determine suitability criteria for dosage forms of medicines for children, with particular attention to conditions prevailing in the developing countries

Comments were received by the Subcommittee from Dr Sabine Kopp, representing the WHO Expert Committee on Specifications for Pharmaceutical Preparations, who discussed the development of a working paper entitled Development of paediatric medicines: pharmaceutical development, points to consider. A number of drafts had already been prepared and revised, following several comments that had been received. It was also noted that an informal working group had been established in collaboration with the National Institute of Child
Health and Human Development, National Institutes of Health, USA, and others to ensure that the ongoing work of the Subcommittee satisfies the above terms of reference, particularly with regard to determining suitability criteria for dosage forms of medicines for children.

During its review of the EMLc, the Subcommittee identified a list of adult preparations that are frequently prepared extemporaneously for administration to children (Table 1). The Subcommittee recommended development of a set of guidelines on the use of extemporaneous preparations in children, including highlighting those medicines (not listed) that should never be prepared in an extemporaneous manner.

**Table 1. Common extemporaneous preparations**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Existing form</th>
<th>Extemporaneous preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>Ear drops</td>
<td>Compounded</td>
</tr>
<tr>
<td>Anti-neoplastic medicines</td>
<td>Various</td>
<td>Preparation of lower dose forms or forms for alternative routes of administration</td>
</tr>
<tr>
<td>Artemether + lumefantrine</td>
<td>Tablet</td>
<td>Crushed tablet</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Tablet</td>
<td>Crushed for oral liquid</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Capsule</td>
<td>Opened for administration as liquid</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>Tablet</td>
<td>Administered as liquid</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Eye drop</td>
<td>Combined with injection for higher strength</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Tablet</td>
<td>Administered as liquid</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Tablet</td>
<td>Administered as liquid</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Liquid form</td>
<td>Administered rectally</td>
</tr>
<tr>
<td>Levothyroxine, propylthiouracil</td>
<td>Tablet</td>
<td>Administered as liquid</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Injection</td>
<td>Administered as oral liquid</td>
</tr>
<tr>
<td>Morphine</td>
<td>Oral, injection</td>
<td>Preparation of liquids, dilution of injection</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>Various</td>
<td>Preparation of different strengths/formulations</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Injection</td>
<td>Administered as liquid</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Tablet</td>
<td>Administered as liquid</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Tablet</td>
<td>Administered as liquid</td>
</tr>
<tr>
<td>Sulfadoxine + pyrimethamine</td>
<td>Tablet</td>
<td>Crushed for liquid</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Tablet</td>
<td>Administered as liquid</td>
</tr>
</tbody>
</table>

This report of the Subcommittee clearly reflects that work addressing suitability criteria for dosage forms is under way but is still far from complete. It was noted that specific recommendations for additions or amendments to the List were driven in large part by products that were identified as available in highly developed countries, with the assumption that they would be adopted and/or readily accepted for procurement or manufacture by developing countries. The Subcommittee also identified significant information gaps and research issues related to further development of dosage forms. In the absence of a mandate or mechanism for the Subcommittee to take the next steps to address these challenges, its recommendations must be considered, at this juncture, as suggestions for continued work by WHO.
**Term of reference 3** – to review the feasibility of manufacturing appropriate formulations for those priority medicines for which no dosage form for children currently exists, specifically considering requirements for use in resource-limited settings and availability of data on efficacy and safety in the appropriate age groups

As regards this term of reference, the Subcommittee has achieved only a conceptual beginning. The recommendations made reflect expert opinion offered in the hope of providing direction to WHO that would enable it to leverage the resources required to ensure that appropriate paediatric medicine products are formulated and made widely available. When possible, specific recommendations for formulations were made (e.g. concentrations of drugs in parenteral solutions appropriate for use in neonates and young infants). The Subcommittee emphatically supports the need to address rational therapeutic use of these formulations and also, careful and critical assessment of their efficacy and safety. Furthermore, considerations of product safety must take into account not only the active ingredients but also excipients that may have intrinsic pharmacological activity.

**Term of reference 4** – to identify the clinical-research gaps regarding safety and efficacy of essential medicines for children in order to improve suboptimal prescribing and dosing, and to facilitate regulatory approval of paediatric formulations

The Subcommittee identified and prioritized clinical research and information gaps related to paediatric therapeutics, ranging from product availability to considerations of medicine selection and therapeutic use. Specific recommendations are provided in Boxes 1–4.

Box 1 lists areas in paediatric therapeutics where more information is clearly needed in order to consider further expansion of the EMLc so that the need for additional medicines for children can be met. Specific recommendations for systematic reviews and evidence syntheses to be conducted and then evaluated by the Subcommittee or the Expert Committee are listed with relative priority designated (H – high; M – medium and L – low). These are generally listed in the order of the sections of the Model List.
Box 1. Evidence syntheses/systematic reviews required

1. Appropriate medicines for pre-operative use in children H
2. Appropriate medicines for use in short-term procedures (conscious sedation) in children H
3. Review use of methylene blue in children M
4. Review use of oral iron/lead chelators M
5. Appropriate medicines for use in resuscitation in children H
7. Essential medicines for management of neuropathic pain in children including the role of lamotrigine, amitryptiline and gabapentin H
8. Essential medicines for management of juvenile inflammatory arthritis L
9. Review of safety and effectiveness of penicillamine compared to sodium calcium edentate L
10. Review of safety and effectiveness of anthelminthics in children H
11. Antimonials as essential medicines for leishmaniasis (core/complementary) H
12. Safety and efficacy of streptomycin in childhood tuberculosis H
13. Other questions identified in the report on tuberculosis medicines H
14. Essential cytotoxic therapies for the commonest tumours in childhood M
15. Review of safety/toxicity of gentian violet L
16. Safety of topical antibiotics including tetracycline ointment in neonates H
17. Alternatives to benzyl benzoate for scabies treatment in young children M
18. Identification of essential diagnostic (contrast) agents for use in children L
19. Essential diuretics for use in children H
20. Clinical use of ondansetron in children M
21. Choice and optimal use of laxatives in children H
22. Essential medicines for treatment of mental health conditions in children H
23. Identification of essential vitamin and mineral supplements (including iron and folic acid) especially in children with human immunodeficiency virus/tuberculosis/malnutrition H
24. Review role of leukotriene antagonists in management of childhood allergic rhinitis L

In identifying priorities for immediate action, the Subcommittee concluded that there were several areas where existing data were available and could easily be formulated into proposals for consideration for addition to the EMLc. Specific recommendations for such action are summarized in Box 2 below.
Box 2. Examples of areas where data exist and applications could be immediately developed

1. Application for a non-sedating antihistamine for children (appropriate comparisons)
2. Application for heat stable protease inhibitors (lopinavir/ritonavir) for HIV management
3. Assess two new clinical trials on safety and efficacy of procaine penicillin in neonates
4. Comparison of sulfadiazine and co-trimoxazole in treatment of toxoplasmosis (possible deletion of sulfadiazine)
5. Review of liposomal amphotericin B as treatment of fungal infections in children H.
6. Applications for amiodarone, lignocaine and adenosine for use in children
7. Application for glucagon
8. Development of child-friendly equipment for medicine administration in sizes for all ages

Discussion emanating from the meeting of the Subcommittee revealed that there were unanswered questions arising from each application. It was also considered likely that the evidence syntheses and systematic reviews listed in Box 1 will produce additional research questions. These information gaps will require the conduct of specific research targeted to critical areas in paediatric therapeutics. A list of highlighted research issues identified during both meetings of the Subcommittee and at the research consultation held in October 2007 is contained in Box 3 below.

Box 3. Research gaps

1. Safety and efficacy of meropenem in neonates
2. Safety and efficacy of protease inhibitors in children weighing less than 10 kg
3. The use of rifabutin and rifapentine for children with tuberculosis co-infection in HIV
4. The role of pharmacotherapy, including amitriptyline, lamotrigine and gabapentin, in management of neuropathic pain
5. International controls over medicines used in palliative care and the need to allow better access in situations of medical need, including use in children
6. Malaria treatments, including fixed-dose combinations that are appropriate for children
7. Treatments for Chagas disease – need for safer treatment
8. Access to insulin
9. Supply chain issues relevant to the EMLc
10. Delayed adverse effects, especially effects on development
11. Factors that modify dose–response relationships in individuals and populations

In developing the updated EMLc, the Subcommittee identified the following specific products (Box 4) as being potentially useful for treatment of children. This is, however, not to be considered as a complete or exhaustive list as it is anticipated that in future deliberations of the Expert Committee additional paediatric products will be identified.
Box 4. Product gaps

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Boosted heat-stable protease inhibitor fixed dose combinations based on existing products and appropriate dosage forms (e.g. sprinkles)</td>
</tr>
<tr>
<td>2.</td>
<td>Inhaled beta-agonists and corticosteroids</td>
</tr>
<tr>
<td></td>
<td>– smaller packaging</td>
</tr>
<tr>
<td></td>
<td>– affordable canisters</td>
</tr>
<tr>
<td>3.</td>
<td>Prostaglandin E oral formulation</td>
</tr>
<tr>
<td>4.</td>
<td>Amphotericin B – appropriate strength for neonates</td>
</tr>
<tr>
<td>5.</td>
<td>Appropriate insulin dosage forms for neonates</td>
</tr>
<tr>
<td>6.</td>
<td>Appropriate strengths of oral and injectable morphine formulation for neonates</td>
</tr>
<tr>
<td>7.</td>
<td>Oral liquid form of hydrocortisone</td>
</tr>
<tr>
<td>8.</td>
<td>Mefloquine liquid formulation</td>
</tr>
<tr>
<td>9.</td>
<td>Pyrimethamine liquid formulation</td>
</tr>
<tr>
<td>10.</td>
<td>Chlorhexidine digluconate 7.1%</td>
</tr>
<tr>
<td>11.</td>
<td>Phenobarbital sodium solution – appropriate strength and alcohol-free formulation</td>
</tr>
<tr>
<td>12.</td>
<td>A multivitamin preparation suitable for general use in neonates and young children</td>
</tr>
<tr>
<td>13.</td>
<td>An accessible, palatable and affordable preparation of zinc salts</td>
</tr>
</tbody>
</table>

As with the issues of paediatric formulations, the guidance given to the Secretariat regarding research priorities is, at present, directional as opposed to strategic. The Subcommittee further identified that for these clinical information and research gaps to be adequately addressed, it will be required that the areas of expertise represented by the current Subcommittee have an effective and dynamic interface with the working groups at WHO that are charged with developing treatment guidelines. Proof-of-concept for the utility of such an approach was offered by the example of recent efforts to address the development of a suitable fixed-dose formulation containing three drugs identified as standards of care for the treatment of tuberculosis in infants and children in the developing world.

**Term of reference 5 – to report to the Expert Committee on the Selection and Use of Essential Medicines in 2009**

The Subcommittee was pleased to report that significant progress had been made in the further development of the EMLc. The list had increased definition and expanded content, driven by the assessment of objective evidence. Two new sections are recommended: medicines for ear, nose and throat disease and medicines specifically for neonatal care. The first of these sections includes topical preparations needed for the management of ear, nose and throat disorders, conditions which are common in children throughout the world and cause significant morbidity, which were not included elsewhere in the EMLc.

In recognition of the high burden of disease occurring in neonates and young infants, the Subcommittee considered the preparation of an essential medicines list for neonates. The Subcommittee proposed adding a section to the EMLc that specifies medicines that are uniquely required for the treatment of neonates. An annex listing medicines from the EMLc that were felt to be essential in treating a variety of neonatal conditions was also provided. In addition, medicines have been proposed for inclusion under the heading of palliative care.
Appropriate utilization of medicines on the EMLc will require purposeful and careful coordination with WHO programmes engaged in the development of treatment guidelines for children. This recommendation is offered as a direct result of the Subcommittee being aware that there are existing treatment guidelines which are not aligned with the best available evidence (1). It is the contention of the Subcommittee that the EMLc can and must be used to support the continued development of paediatric-specific treatment guidelines for a variety of conditions and diseases. The Subcommittee also asserts that is critical that the work undertaken thus far continues. Specifically, WHO should take a comprehensive, translational approach towards paediatric therapeutics, which focuses clearly on medicine use and the assessment of safety and efficacy associated with drug treatment. To attain this goal for the benefit of children around the world will require continuity of effort, widened engagement of professionals with paediatric expertise that spans the continuum of drug therapy (e.g. formulation development, drug delivery, clinical pharmacology and paediatric medicine) and adoption of a strategy that continues to place a priority on the value of providing children in all countries with the right to a healthy life.

Finally, the Subcommittee discussed the most effective and efficient mechanism to provide the continuity and level of engagement required to achieve the above-mentioned objectives.

To this end, the following recommendations are offered to the Expert Committee for consideration:

1. This report of the Subcommittee will be tendered to the Expert Committee for consideration, deliberation and adoption at the meeting to be held in March 2009.

2. For the foreseeable future, it is essential that the EMLc remain separate from the WHO Model List of Essential Medicines in order to maintain a critical focus on the needs of children.

3. The Secretariat should use available resources necessary to undertake reviews recommended by the Subcommittee and also to address information and research gaps of high priority for the paediatric medicines initiative. This may be done through the development of specific contracts and/or the establishment of strategic working groups that might be focused on a specific issue.

4. Consideration should be given to the appropriate constitution of future Expert Committees in order to meet the demands of United Nations Millennium Goals 4 and 6 to focus on paediatric priorities and Resolution WHA60.20. This would include further development and expansion of the EMLc and establishing plans for its continued maintenance.

5. To meet the critical needs of improving paediatric therapeutics throughout the world through an evidence-based approach, it is imperative that WHO continue to work effectively to define and address research gaps. Most importantly, WHO should create approaches to generate the new knowledge necessary for translation of discovery into rational therapeutic practices.
4. The WHO Model List of Essential Medicines for Children – by section

Section 4. Antidotes and other substances used in poisonings

Section 4 of the Model List of Essential Medicines concerns medicines used as antidotes and for the management of poisonings. The Subcommittee had requested further evaluation of the burden of disease and disability in children due to poisoning as well as applications for specific antidotes deemed critical for children. The Secretariat had therefore commissioned reviews of two key antidotes already on the Model List and the preparation of an application for inclusion of pralidoxime.

Comments were received from the South Asian Clinical Toxicology Research Collaboration and the WHO Department of Protection of the Human Environment.

Section 4.1 Non-specific

Charcoal, activated (review)

Core list

The Subcommittee considered the review of activated charcoal for the treatment of non-specific poisoning in children. The review was commissioned by the Secretariat and provided by Dr Jennifer A. Lowry from the University of Missouri-Kansas City and Children’s Mercy Hospital, USA. Expert review comments were provided by Dr Helena L. Coelho and Professor N. Cranswick.

Accidental poisonings in children are a significant problem, particularly throughout the developing world. The Subcommittee noted that there is a paucity of high-quality evidence for the efficacy of activated charcoal in children, and that the majority of the literature is based on a collection of case-series and case-reports in adult patients. Position statements from the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists were reviewed. They suggested that activated charcoal is most effective when given within the first hour following the ingestion of a poison, and that multi-dose activated charcoal should only be used following specific ingestions. The Subcommittee also considered comments from the South Asian Clinical Toxicology Research Collaboration which supported the inclusion of activated charcoal in the EMLc.

The Subcommittee considered that despite the limited evidence from controlled clinical trials for the efficacy of activated charcoal in children, when considered on balance with the low risk of adverse reactions and the limited alternatives for gastric decontamination, activated charcoal should remain on the EMLc.
Section 4.2 Specific

**Acetylcysteine (review)**

The Subcommittee reviewed the inclusion of N-acetylcysteine (NAC) on the EMLc as an antidote for paracetamol (acetaminophen) toxicity. A systematic review was commissioned by the Secretariat and provided by Dr D. Adam Algren from the University of Missouri-Kansas City and Children’s Mercy Hospital. The expert comments were provided by Mrs Jenna Mohammed Ali Al-Fannah and Dr Helena L. Coelho. Comments were noted from members of the South Asian Clinical Toxicology Research Collaboration who supported the inclusion of oral NAC on the EMLc.

The review summarized the clinical evidence for use of NAC in adults and noted that no randomized efficacy trials have been conducted in children. There is significant clinical evidence in adult populations to suggest that oral and intravenous NAC are equally effective. The intravenous form of NAC can also be administered orally. A small study involving 25 paediatric patients demonstrated comparable efficacy between intravenous and oral NAC. Several observational studies involving the use of oral NAC showed a decrease in the incidence of hepatotoxicity in those patients in whom NAC therapy was initiated within 10 hours of ingestion. However, these studies involved only small numbers of paediatric patients.

The Subcommittee noted that the major concern with regard to adverse effects in children is that intravenous infusion in children may be associated with hyponatraemia if excessive fluids are administered in conjunction with NAC and also, anaphylactoid reactions are associated with the parenteral formulation.

The Subcommittee agreed that NAC is considered the treatment of choice for paracetamol toxicity where the dose and/or paracetamol plasma concentrations would suggest the risk of serious hepatotoxicity from an acute ingestion. It was agreed that intravenous NAC should remain on the List, and that the oral form should be added. The proposed WHO Model Formulary for Children may need to contain advice on appropriate use, including guidance on initiation of therapy and avoidance of unnecessary administration in the situation of sub-toxic doses of paracetamol.

**Pralidoxime (inclusion)**

*Core list*

The Subcommittee considered the proposal for inclusion of pralidoxime for the treatment of organophosphate poisoning in children. Expert comments were provided by Professor H.P.S. Sachdev. Atropine is currently the only antidote on the EMLc for acute organophosphate poisoning.

The Subcommittee noted that information on the prevalence of acute organophosphate poisoning in children is limited, although it is known to be an increasing problem worldwide, particularly in rural regions of developing countries.
The Subcommittee considered the evidence for the safety and efficacy of pralidoxime provided in the proposal. The proposal was based on five systematic reviews of studies involving adult patients (2, 3, 4, 5, 6). There were no data in these reviews which described the use of pralidoxime in children. The study designs were of variable quality. Collectively, the data from the adult studies were unable to conclusively establish the effectiveness of pralidoxime in the treatment of organophosphate poisoning. The Subcommittee was made aware of two case-series describing the use of intravenous pralidoxime in children with organophosphate poisoning (7, 8).

Comments from the South Asian Clinical Toxicology Research Collaboration, which had been involved in a large randomized controlled trial of pralidoxime in Sri Lanka, were noted: the Collaboration stated that data analysed thus far did not provide supporting evidence for the inclusion of pralidoxime in the EMLc.

The Subcommittee considered that at this time there was insufficient evidence to justify the inclusion of pralidoxime on the EMLc. It recommended that new trial data and the additional paediatric data be considered in March 2009.

For further revision of this section, the Subcommittee recommends the future consideration of additional iron and lead chelating agents and methylene blue as potential essential antidotes for paediatric use.

**Section 6. Anti-infective medicines**

At its first meeting in July 2007, the Subcommittee identified a number of questions about anti-infective medicines for children that needed further review. These included the need to obtain additional evidence and safety about products already on the EMLc as well as applications for new products.

**Section 6.2 Antibacterials**

**Section 6.2.1 Beta-lactam medicines**

The Subcommittee considered reviews of efficacy and safety for procaine benzylpenicillin, ceftazidime and ceftriaxone, the carbapenems as a class, and a new application for cefelaxin.

Expert comments on the proposals were prepared by Mr Andy Gray, Dr Kalle Hoppu, Professor Prakash Mohan Jeena, Dr Peter Kazembe, Professor Harshi Sachdev, Dr Anita Zaidi and Dr Elizabeta Zisovska.

Comments were received from the WHO Department of Child and Adolescent Health and Development.

**Cefalexin (inclusion)**

A new proposal, commissioned by the Secretariat, for the inclusion of cefalexin on the EMLc was considered. Expert comments on cefalexin were provided by Mr Andy Gray and Dr Kalle Hoppu. It was noted that the WHO Department of Child and
Adolescent Health and Development had suggested inclusion of cefalexin on the Complementary List.

The Subcommittee noted that the Expert Committee had previously considered an application for the addition of cefazolin and cefalexin in March 2007. At that time, cefazolin was added to the EMLc based on the high quality clinical evidence for its use in surgical prophylaxis. The proposal for cefalexin, on the other hand, was rejected on the basis of the limited evidence for its comparative effectiveness over other antibiotics already included on the EMLc, and concerns about inappropriate prescribing.

The new proposal stated that first-generation oral cefalosporins are generally inexpensive, easy to administer and commonly used in community outpatient settings. They provide good cover against the common organisms (e.g. Staphylococcus aureus and streptococci) that cause uncomplicated community-acquired respiratory, skin and soft tissue infections; however evidence for superiority over other antibiotics is limited.

The Subcommittee noted that evidence for clinical efficacy and safety of cefalexin in children was limited. Evidence presented in the proposal included a Cochrane systematic review (9) of 16 studies for the treatment of impetigo, which included both children and adults. Other trials (10, 11) using cefalexin for the treatment of Group A streptococcal pharyngitis in children and adolescents showed equivalent clinical cure rates for cefalexin and penicillin. The efficacy of cefalexin in the treatment of urinary tract infections without proven culture sensitivity has not been demonstrated, and there are insufficient data available on the use of cefalexin for prevention of rheumatic fever or carditis.

After considerable deliberation, the Subcommittee found potential merits associated with the availability of cefalexin. These included evidence of effective treatment of skin and soft tissue infections produced by a variety of pathogens (with the exception of methicillin-resistant Staphylococcus aureus), the treatment of uncomplicated urinary tract infections produced by sensitive pathogens, and the perception that better palatability is associated with improved adherence to treatment regimens, particularly for prolonged treatment such as in the case of osteomyelitis. Also, it was recognized that cefalexin can often be safely administered to patients who demonstrate hypersensitivity reactions to penicillin. The Subcommittee therefore added cefalexin to the EMLc Core List.

Procaíne benzylpenicillin (review)

The Subcommittee considered the review of procaine benzylpenicillin in neonates. The Subcommittee had previously raised concerns in October 2007 about its safety and efficacy in neonates, despite its widespread use in this age group. Expert reviews were provided by Dr Stuart MacLeod and Dr Gregory Kearns.

It was noted that (crystalline) benzylpenicillin is the preferred agent for treating serious infections such as neonatal sepsis and congenital syphilis. However several
sets of guidelines (e.g. those of the American Academy of Pediatrics and the CDC Sexually Transmitted Diseases Treatment Guidelines) recommend intramuscular procaine benzylpenicillin as an alternative for use in the management of proven congenital syphilis. Only one randomized controlled trial demonstrating a significant reduction in rapid plasma reagin (RPR) titres, following treatment for congenital syphilis with either procaine benzylpenicillin or benzathine benzylpenicillin, was included in the review (12).

The Subcommittee noted that although the WHO Pocket book of hospital care for children recommends intramuscular procaine benzylpenicillin in combination with gentamicin as an alternative treatment to (crystalline) benzylpenicillin for the management of neonatal sepsis and meningitis in neonates, there is no evidence for the efficacy of procaine benzylpenicillin in the management of early onset Group B sepsis, or in the community management of sepsis and pneumonia in neonates. It was also noted that procaine benzylpenicillin has low cerebrospinal fluid penetration and, therefore, may be ineffective in treating infants who develop, or who are at risk of developing, bacterial meningitis. However, the Subcommittee also noted that procaine benzylpenicillin has been used as an alternative to (crystalline) benzylpenicillin as it can easily be administered in the community with once daily intramuscular dosing.

The Subcommittee took account of the safety concerns regarding the intramuscular administration of procaine benzylpenicillin in premature and low-birth-weight infants, including the reports of injection-site abscesses, muscle fibrosis and atrophy following intramuscular injection, particularly in premature and low birth weight neonates.

The Subcommittee noted that current studies of procaine benzylpenicillin given in combination with gentamicin as first-line treatment for infants with Gram-positive infections are underway and the results will be considered when they become available. The Subcommittee recommended: removal of the age restriction for procaine benzylpenicillin; a note added that it is not recommended as first-line treatment for sepsis and/or meningitis; but requested a further review of safety.

**Ceftazidime (review)**

*Complementary List*

The Subcommittee reviewed the inclusion of ceftazidime on the Complementary List. Expert comments were provided by Professor Prakash Mohan Jeena. In July 2007, the Subcommittee had identified the need to determine whether there were preferred alternatives for use in children.

It was noted that the review found limited evidence on efficacy and safety of use of ceftazidime in children and similarly limited information about the treatment of *Pseudomonas aeruginosa* in children. The main source of information was a systematic review of 57 trials comparing cefepime with other antibiotics, but only two had
compared ceftazidime to cefepime in children: one was in patients with febrile neutropenia, the other in patients with urinary tract infections (13).

The Subcommittee noted that there was no clinical evidence for the superiority of one antibiotic over the other for the treatment of *Pseudomonas aeruginosa* in cystic fibrosis, or as empirical treatment for ventilator-assisted pneumonia, and that ceftazidime was the antibiotic of choice in the treatment of *Burkholderia cepacia* infections in cystic fibrosis and of *Burkholderia pseudomallei* infections.

The Subcommittee also noted that there are no recommended age restrictions for the use of ceftazidime, and that it is the least expensive of the anti-pseudomonal antibiotics according to the International Drug Price Indicator Guide.

The Subcommittee agreed that although there was no evidence to support the superior efficacy or safety of ceftazidime over other antibiotics with a similar antibacterial spectrum, the drug should remain on the Complementary List of the EMLc.

### Ceftriaxone

In response to safety concerns raised at the first meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines in 2007, the Secretariat commissioned a review of the use and safety of ceftriaxone in neonates. Expert comments were provided by Professor H.P.S. Sachdev and Dr Elizabeta Zisovska.

The review identified four trials that had studied the use of ceftriaxone in neonates, for the treatment of sepsis and meningitis. The review noted that ceftriaxone can cause significant adverse reactions in neonates, including: a potentially fatal interaction with calcium; superinfections with candida and non-susceptible bacteria such as extended spectrum beta-lactamase producers; and kernicterus.

The Subcommittee considered whether the use of ceftriaxone should be contraindicated in premature infants younger than 41 weeks total age and the use restricted to infants ≥ 1 month of age. The Subcommittee noted that safety warnings had been issued by several regulatory authorities and Roche regarding interactions between ceftriaxone and calcium. Due to precipitation that can produce severe adverse effects, the administration of calcium and ceftriaxone in the same or different infusion lines or sites must be avoided. While current information suggests that a 48-hour period between administration of ceftriaxone and calcium is required, altered pharmacokinetics of the drug in neonates may require an even longer period separating the administration of the two drugs. Ceftriaxone use should be avoided in neonates with hyperbilirubinaemia consequent to potential disruption in bilirubin protein binding and the production of biliary sludging.

The Subcommittee recognized that a minimum age restriction was required for this medicine and therefore recommended that a note be inserted in the EMLc to restrict use to infants older than 41 weeks corrected gestational age. The use of ceftriaxone
should be restricted to those who are being discharged from hospital who still require parenteral antimicrobial treatment and will not be receiving concomitant calcium treatment.

The Subcommittee also considered whether the medicine should be moved to the Complementary List, but on balance, decided to retain it in the Core List because of the importance of rapid treatment for meningitis at first-line health-care facilities. Given the significant safety concerns associated with the use of this medicine in neonates, it was recommended that the Advisory Committee on Safety of Medicines evaluate the use of ceftriaxone in infants and children at its next meeting.

**Carbapenems (review)**

**Complementary List**

The Subcommittee considered the review of carbapenems, which was commissioned following the 2007 meeting to identify potential alternatives to the currently listed imipenem–cilastatin. Expert comments were provided by Dr Anita Zaidi.

The Subcommittee noted that the majority of evidence for the safety and efficacy of meropenem and imipenem–cilastatin comes from a systematic review of studies in adults, which demonstrated that meropenem produced a marginally better clinical and bacteriological cure rate than imipenem (14). The limited evidence from studies in children suggested that the efficacy and safety of meropenem and imipenem–cilastatin were comparable for most indications other than meningitis (15). The Subcommittee noted that meropenem was the only carbapenem that could be used for treatment of meningitis, due to its low propensity to cause seizures even at high doses. Imipenem–cilastatin is contraindicated for meningitis.

Although the cost of meropenem is higher than that of comparators, the Subcommittee took into account that studies done in the Russian Federation, the UK and the USA have shown that the overall cost of therapy for patients with severe infection in intensive care units is lower for meropenem than for imipenem–cilastatin and conventional combination antibacterial therapy (16).

The Subcommittee noted that meropenem is not currently licensed for neonates. While the *British National Formulary* (BNF) for Children 2008 does give dosages for meropenem in neonates, these recommendations do not appear to be firmly supported by data from controlled clinical trials of pharmacokinetics or drug safety in this subpopulation. Imipenem–cilastatin is the only carbapenem currently approved by regulatory authorities for use in all age groups.

The Subcommittee recommended that for all infections caused by drug-resistant pathogens known or believed to be sensitive to a carbapenem, meropenem can be considered as an alternative to imipenem–cilastatin. Given its association with the production of seizures, imipenem–cilastatin is contraindicated for use in infants and children with meningitis. In such situations, meropenem is the preferable agent. Until complete data on meropenem in young infants and neonates are available, it is
recommended that imipenem–cilastatin be retained on the EMLc but that a note should be inserted to recommend the use of meropenem where appropriate.

Section 6.2.2 Other antibacterials

Macrolides
At the meeting of the Subcommittee in July 2007, the question of differences in efficacy and safety between the macrolides, particularly with regard to their use in neonates, was raised. It was also noted that, with the exception of the treatment of trachoma, there was no evidence for the superiority of azithromycin over other macrolides or beta lactams. It was therefore decided that azithromycin should remain restricted to the specified indication of trachoma and that a review should be commissioned by the Secretariat to summarize the evidence regarding the use of macrolides in children, with particular regard to safety and efficacy in neonates. Azithromycin and erythromycin were the only macrolides on the EMLc.

Expert review comments were provided by Mrs Jehan Mohammed Ali Al-Fannah and Dr Jacqueline Deen.

Comparative evidence for efficacy
There is no evidence for the superiority of azithromycin over other macrolides for the treatment of *Bordetella pertussis* or *Campylobacter jejuni*. However guidelines from the American Academy of Pediatrics and the Centers for Disease Control and Prevention (CDC) recommend azithromycin as the preferred macrolide for treatment of *Bordetella pertussis* infections. Azithromycin is the macrolide of choice for trachoma treatment in children older than six months, and the efficacy of azithromycin for the treatment of trachoma has been demonstrated in several randomized controlled trials identified in the review. This is consistent with the current recommendation in WHO guidelines (17).

A Cochrane review (18) did not find any evidence for the superiority of azithromycin in the treatment of community-acquired pneumonia over other antibiotics such as amoxicillin–clavulanic acid or erythromycin. There is no evidence that azithromycin is superior to other antibiotics for the treatment of Legionnaires’ disease, acute otitis media or sinusitis.

Clarithromycin is recommended for the treatment and prophylaxis of disseminated *Mycobacterium avium intracelluarum* infection in children infected with HIV according to the US CDC guidelines. However data on the use of clarithromycin in children are scanty and it is not recommended for this indication in children aged less than 20 months. It may also be effective for the treatment of pertussis, Legionnaires’ disease, and *Helicobacter pylori* but there is no evidence for its superiority over the other macrolides.

Comparative evidence for safety
Erythromycin is administered 3 or 4 times per day. Azithromycin is administered as a single daily dose. Adverse events reported for erythromycin may include epigastric distress, hepatic dysfunction and drug interactions. In neonates, its use may be
associated with infantile hypertrophic pyloric stenosis (IHPS) that may be dose-dependent, and occurs at a rate of between 5 and 10%. For this reason, other macrolides have often been recommended for use in neonates despite the absence of strong evidence for their safety or efficacy in this age group. Intravenous use of erythromycin has been associated with thrombophlebitis, cardiac arrhythmias, and auditory impairment. There are no systematic reviews comparing the tolerability of erythromycin with that of other macrolides.

The Secretariat identified four trials that directly compared azithromycin with erythromycin and reported adverse effects: two from the Cochrane review of antibiotics for community-acquired pneumonia in children (19, 20), one from the Cochrane review of antibiotics for pertussis (21) and the fourth, a trial by Langley et al. (22), not included in either review, by far the largest direct comparison of azithromycin with erythromycin in the treatment of pertussis in 477 children.

As reported in the study by Langley et al. (22), the clinical and bacterial efficacy of the two treatments was the same. However gastrointestinal events were reported significantly more frequently in the group treated with erythromycin (41.2%) than in the group that received azithromycin (18.8%). Children randomized to azithromycin were also much more likely to have complied with antimicrobial therapy during the treatment period (90% versus 55%).

Only one study directly comparing clarithromycin with erythromycin was found (23) in which clarithromycin was shown to lead to significantly fewer adverse events (34/76) than erythromycin (48/77, p = 0.035).

Comparative evidence in neonates
Erythromycin has been approved for use in neonates for the treatment of eye infections and pneumonia caused by Chlamydia trachomatis.

Azithromycin has not been approved for use in children under six months old, and evidence for its efficacy and safety is limited to a single study of 13 neonates, which found azithromycin to be effective and safe in this age group. Guidelines from the CDC and the American Academy of Paediatrics recommend the use of azithromycin in children under one month for the treatment of Bordetella pertussis infections.

Clarithromycin is not licensed nor recommended for use in neonates.

Currently, the cost of azithromycin is US$ 0.53/DDD, that of erythromycin US$ 0.10/DDD and of clarithromycin US$ 0.44/DDD for solid dosage forms based on the Management Sciences for Health International Drug Price Indicator Guide.
The Subcommittee noted that:

- Azithromycin remains the antibiotic of choice for the treatment of trachoma.
- The drug interaction profile for the macrolides differs with erythromycin and clarithromycin producing inhibition of CYP3A activity sufficient to alter the pharmacokinetics of drugs that are CYP3A4/5 substrates. Azithromycin appears to be devoid of drug interactions with CYP3A substrates.
- There remains limited evidence for the superiority of one macrolide over another in the management of other infections. They are best considered as clinically interchangeable in terms of efficacy.
- There are minimal data on the comparative safety of the macrolides. Azithromycin is favoured, but this is not clinically significant.
- The available data on efficacy and safety of macrolides in children under six months are primarily for erythromycin; data for azithromycin and clarithromycin in children younger than six months are scanty. Despite this lack of quality evidence, guidelines from the CDC and the American Academy of Pediatrics continue to recommend the use of azithromycin in children in this age group for the treatment and prophylaxis of Bordetella pertussis, as azithromycin may be better tolerated and easier to administer. There is the potential for resistance to develop if azithromycin is overused or used inappropriately.

It was therefore agreed that azithromycin remain on the EMLc with a note regarding its appropriate indication, that oral erythromycin be retained, but without annotation, and that intravenous erythromycin be deleted.

**Fluoroquinolones (review)**

In 2007, the Subcommittee reviewed the listing of fluoroquinolones for use in children and, given the concerns about the potential for the overuse and inappropriate use of fluoroquinolones outside the recommended indications, a review on the efficacy, safety and rational use of fluoroquinolones in children was requested. Expert comments were provided by Professor Dai Yao Hua and Dr Jacqueline Deen.

The review commissioned by the Secretariat cited a Cochrane review of quinolones for treatment of typhoid fever (24) in which three of the trials were exclusively in children (comparisons were: ofloxacin with cefixime, norfloxacin with ceftriaxone, and ofloxacin for two versus three days). The overall conclusion of the Cochrane review was that there was no evidence for the superiority of quinolones in the treatment of typhoid fever in children over other antibiotics such as ceftriaxone or cefixime.

It was noted that evidence for the use of oral ciprofloxacin in the management of shigella, salmonella and other gastrointestinal infections consists mostly of case-series and case-reports. The Zimbabwe, Bangladesh, South Africa Study group has
conducted a multicentre, double-blind randomized controlled trial (25) in which 235 children with shigella were randomly assigned to receive oral ciprofloxacin for a 3- or 5-day course. All children were microbiologically cured and all isolates were sensitive to ciprofloxacin. Several countries have recently reported increased resistance to fluoroquinolones in the management of these conditions.

No randomized controlled trials evaluating efficacy of a fluoroquinolone in the management of meningitis in children were identified, and data on clinical efficacy of fluoroquinolones in neonates and pre-term infants are scanty. An additional search of the literature undertaken by the Secretariat identified two further studies not included in the review: a matched case–control study (26) in which 30 neonates were treated with parenteral ciprofloxacin for 14 days. When controlled for birth weight and gestation, cartilage size was not affected by ciprofloxacin. The second, a prospective long-term follow-up study carried out in Bangladesh (27) and involving 48 preterm infants of less than 33 weeks gestation concluded that ciprofloxacin was a safe therapeutic option for newborns with sepsis produced by multi-resistant organisms, with no differences in growth and development observed in the ciprofloxacin-treated group during treatment or follow-up.

It was noted that there are no data comparing the superiority of the other quinolones such as gatifloxacin and moxifloxacin over ciprofloxacin in children.

The application included a review of the findings in animals and compared this to a summary of findings in children (31 reports, > 7000 children) where arthropathy was found to be reversible, without long-term sequelae, and not convincingly correlated with the use of fluoroquinolones in children. The Subcommittee noted the recent warnings issued by the US Food and Drug Administration about the risk of arthropathy in adult patients older than 65 years and the risk of tendon rupture associated with protracted treatment in adults over 60 years of age.

The Subcommittee agreed that:

– Evidence for the clinical efficacy and superiority of fluoroquinolones over other antibiotics in children is limited, particularly within the neonatal and preterm period.
– Ciprofloxacin remains the fluoroquinolone for which there is the most evidence for use and safety in children.
– Inappropriate use of fluoroquinolones has the potential to rapidly increase the emergence of resistance.

The Subcommittee concluded that sufficient evidence is available to support the use of ciprofloxacin as a second-line treatment for specific, severe infections in paediatric patients. Given patterns of use, it was decided that ciprofloxacin should remain the only fluoroquinolone on the EMLc as there is evidence for ciprofloxacin to be used in other infections. The statement regarding Shigella should be deleted. It was also recommended that the safety issues pertaining to use of fluoroquinolone in neonates
and children be considered by the Advisory Committee on the Safety of Medicines at its next meeting.

**Tetracycline (review)**

The use of tetracyclines in children was reviewed by the Subcommittee. The inclusion of tetracycline on the EMLc for use in treating severe cholera had previously been reviewed by the Subcommittee in July 2007, at which time the square box had been deleted as there was no evidence to support the use of other tetracyclines for this indication. The Secretariat was requested to commission a review to address this question. Expert comments were provided by Professor Tony Nunn.

The evidence identified in the review for the efficacy of tetracyclines in treating children was mostly gathered in children over 8 years of age, and the majority of the available evidence is for the use of doxycycline. No evidence was found for the use of other tetracyclines in the management of severe cholera.

The Subcommittee recognized that doxycycline and tetracycline have been recommended as the treatment of choice in Rickettsial infections. The reviewers cited a Cochrane review of therapy for scrub typhus involving four trials, which demonstrated no difference between the use of doxycycline and tetracycline, or between tetracycline and chloramphenicol in the management of scrub typhus (28).

Minimal evidence was identified in the review for the efficacy of tetracyclines in the management of *Mycoplasma pneumoniae*, leptospirosis, or for the prophylaxis against *Plasmodium falciparum* and anthrax in children.

The Subcommittee acknowledged that children under 8 years of age may develop permanent brown discoloration of their teeth, enamel defects and hypoplasia following the use of tetracyclines, which may be related to dose and duration of therapy. It was noted that a small amount of evidence exists that doxycycline may have less adverse effect on teeth than the other tetracyclines. In one study, only six out of 300 children and premature infants exposed to doxycycline developed discoloration of their teeth. A further small study, not identified in the review, showed absence of tooth staining in 30 children aged between 2 and 8 years who received doxycycline treatment (29).

The Subcommittee agreed that doxycycline is a useful antibiotic for the management of a wide range of infections as well as in the prophylaxis against infections of public health importance, and therefore removed the restricted indication for cholera. It was noted that evidence for the efficacy and safety of other tetracyclines in children is limited, and therefore agreed that doxycycline be included in the EMLc without a square box. An age restriction (over 8 years) should be applied when the tetracyclines are used to treat non-life-threatening infections.
Gentamicin (review)

The Subcommittee reviewed the inclusion of gentamicin on the EMLc as concerns had previously been raised regarding potential ethnic differences in ototoxicity associated with this drug. Expert reviews were provided by Dr Peter Kazembe and Dr Anita Zaidi.

It was noted that most of the available evidence for the safety of aminoglycosides in children is for gentamicin. The review identified a Cochrane systematic review of 11 studies (n = 574 subjects) (30) that assessed the safety and efficacy of a once-daily dose of gentamicin in neonates less than 28 days old being treated for sepsis. No ototoxicity or nephrotoxicity was seen in any of the patients, however limited numbers of preterm infants were included in these studies.

A second meta-analysis (31) of 24 randomized controlled trials compared once-daily dosing regimens with more frequent dosing in terms of patients with hearing loss (assessed through both clinical and formal auditory testing). There were no cases of clinical hearing impairment; however on auditory testing, 2.3% of children treated with once-daily doses of gentamicin were found to have auditory loss, compared with 2% of children treated with multi-dose administration of gentamicin (10/436 versus 8/406, relative risk 1.16; 95% confidence intervals (CI) 0.48–2.84). The majority of trials included in this meta-analysis were of small sample size, and although the two regimens seemed equivalent with respect to ototoxicity, only half of the studies actually incorporated formal audiometric testing. It was noted that less than 2% of children in either treatment group in this systematic review were found to have primary nephrotoxicity.

Another systematic review of 16 trials (32) comparing daily gentamicin dosing with multi-dosing in neonates aged less than 30 days on initiation of treatment demonstrated only one episode of ototoxicity in 210 neonates. No significant difference in toxicity between the two dosing regimens was seen.

The Subcommittee noted that there is limited evidence for the occurrence of ototoxicity in preterm infants following gentamicin use, although the majority of measurements for toxicity are carried out in the immediate post-treatment period only.

It was noted that toxicity correlates with gentamicin concentration in plasma and with duration of use. The Subcommittee could find no documentation supporting an ethnic predilection for gentamicin toxicity in Chinese populations either within China or in other countries. The Subcommittee agreed that the majority of evidence demonstrates a low incidence of ototoxicity and nephrotoxicity following the use of gentamicin in children, but noted that there is a paucity of evidence for the occurrence of toxicity following aminoglycoside use in preterm infants, or on long-term follow-up. Systematic reviews failed to show a difference in incidence of gentamicin–associated ototoxicity with varying dosing regimens. On balance, given its broad potential for use in infections with Gram–negative organisms, it was agreed that gentamicin should remain as the aminoglycoside on the EMLc.
Sulfadiazine (review)

The Subcommittee considered the review of sulfadiazine for the treatment of toxoplasmosis in children. It had been noted in 2007 that sulfadiazine was not licensed for the treatment of toxoplasmosis in children, and therefore a review of its use in children with particular regard to the treatment of toxoplasmosis was requested. Expert reviews were provided by Dr Stuart MacLeod and Dr Tony Nunn.

Evidence cited in the Secretariat’s review to support the efficacy of sulfadiazine in the management of toxoplasma encephalitis included a Cochrane review (33) and several other randomized controlled trials involving adults with HIV (34), however there was limited evidence for its superiority over trimethoprim–sulfamethoxazole for this indication. Studies of the management of congenital toxoplasmosis included several longitudinal cohort studies (35, 36, 37), which demonstrated sulfadiazine to be an efficacious and safe treatment for infected neonates. An improved outcome was seen in the majority of infected infants who were treated with combination sulfadiazine therapy; however outcome was shown to be dependent on the duration of treatment and the degree of disability at birth. The Subcommittee noted that there was no evidence to support the use of sulfadiazine in the treatment of nocardia or other infections.

Sulfadiazine treatment appeared to be well tolerated, with adverse reactions reported in approximately 5% of patients. No systematic reviews comparing oral versus intravenous sulfadiazine were identified, however it was noted that the majority of guidelines, including the CDC and the British National Formulary 2006, recommend oral sulfadiazine in the management of toxoplasmosis. The majority of an oral dose is rapidly absorbed from the gastrointestinal tract and therefore no justification for an intravenous form could be made.

The Subcommittee agreed that there was sufficient evidence for the clinical efficacy and safety of oral sulfadiazine in children for the treatment of congenital toxoplasmosis. It was decided that intravenous sulfadiazine should be removed from the EMLc and the oral tablet formulation should be deleted from Section 6.2.2 of the EMLc and moved to Section 6.5.4 (antitoxoplasmosis medicines). The need for an oral liquid formulation of sulfadiazine was also identified.

Section 6.2.4 Antituberculosis medicines (review)

At the July 2007 meeting, the Subcommittee noted that the fixed-dose combinations (FDCs) listed for the first-line treatment of tuberculosis in children needed to be reviewed to determine whether the currently recommended strengths were appropriate for children. The Secretariat commissioned a review of pharmacokinetic studies, and this was presented and considered at an informal meeting in July 2008. The report of the meeting is on the Subcommittee web site; the review of pharmacokinetic studies has not yet been published. A review of studies of ethambutol use in children was published in 2006 (38).
The recommendations for doses of pyrazinamide, isoniazid and rifampicin based on the assessment of the medical literature reviewed at the meeting are quoted below:

1. The panel recommends that the dose of PZ in children above 3 months of age should be 35 mg/kg (range 30–40) per day. The maximum daily dose should not exceed the recommended adult daily dose. If data are accessible, further analysis of the IPD from recent PK studies may increase the confidence in this recommendation.

2. The panel recommends that the dose of isoniazid in children above 3 months of age for treatment or prophylaxis (treatment of latent TB infection) should be 10 mg/kg (range 10–15) per day. The maximum daily dose should not exceed the recommended adult daily dose.

3. The panel recommends that the dose of RMP in children above 3 months of age should be 15 mg/kg (range 10–20) per day. Dosages at the higher ranges may be preferable for children under 10 kilograms, and children with HIV infection or malnutrition. The maximum daily dose should not exceed the recommended adult daily dose.

The Subcommittee then considered what type of FDC product would be needed to ensure sufficient flexibility to enable accurate administration of age-specific doses of each component medication. The three-drug formulation proposed at the meeting in July 2008 (isoniazid 100 mg/pyrazinamide 350 mg/rifampicin 200 mg) was considered, but is not endorsed at present. The Subcommittee realizes that additional work is under way, which, when completed, should provide a more refined assessment of what the composition and properties of an ideal formulation should be.

Although the EMLc listed three FDC products for children, no prequalified products existed in the strengths listed. The Subcommittee considered whether the FDCs on the EMLc should be retained. Taking into consideration the public health importance of ensuring that treatment for tuberculosis is effective and noting that no products are currently prequalified, the Subcommittee recommended deletion of the existing FDCs on the grounds of potential underdosing, with the associated risk of treatment failure, and lack of suitability, as multiple tablets of the existing strengths would be needed to ensure effective doses. The Subcommittee supported the urgent need for further research and reviews on this topic to define optimal doses, and recommended that the Expert Committee should consider progress on this at its meeting in March 2009.

Section 6.4.2 Antiretrovirals (new formulations)

At its meeting in 2007, the Subcommittee considered that FDCs for children with HIV were clearly essential and endorsed three FDCs already on the adult list of essential medicines as appropriate for older children (listed in alphabetical order):

- lamivudine + nevirapine + stavudine: 150 + 200 + 30 mg
- lamivudine + nevirapine + zidovudine: 150 + 200 + 300 mg
- lamivudine + zidovudine: 150 + 300 mg.
In addition, the Subcommittee considered but rejected a number of applications for FDC products for the treatment of children with HIV:

- lamivudine + nevirapine + stavudine, 40 + 70 + 10 mg, and 20 + 35 + 5 mg, Ranbaxy
- lamivudine + nevirapine + zidovudine tablet, 30 + 60 + 60 mg, Ranbaxy
- lamivudine + zidovudine, 150 + 300 mg scored tablet, GlaxoSmithKline.

Three new applications were submitted at this meeting, for the following combinations:

- lamivudine + nevirapine + stavudine dispersible tablets 30 + 50 + 6 mg and 60 + 100 + 12 mg, Cipla
- lamivudine + nevirapine + zidovudine tablet 30 + 50 + 60 mg, Matrix Laboratories
- lamivudine + zidovudine tablet 30 + 60 mg, Matrix Laboratories.

Expert reviews were provided by Mr Andy Gray and Dr Peter Kazembe; comments were received from the WHO Department of HIV.

The key problem for specifying FDCs is determining the appropriate doses of the components so that they are suitable for all children. For HIV, “ideal doses” of components for first-line treatment have now been identified by an expert group working with the WHO Department of HIV. These are published on the WHO website. The most recent update of the “ideal dosing table” is at: http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf.

The Subcommittee noted that the two applications from Matrix presented no clinical evidence apart from bioequivalence studies. The applications were based on the recommended doses in the WHO guidelines, and the clinical evidence supporting these recommendations is summarized in an extensive report at: http://www.who.int/hiv/paediatric/External_report_dosing_paediatric_ARVs.pdf.

Both products are consistent with the “ideal products” listed in the dosing table. Both have been registered in India and are under review by the WHO Prequalification Programme.

The application from Cipla was more complete, and as well as summary results of bioequivalence studies, included a limited review of the relevant clinical literature. The doses of the components are consistent with the WHO “ideal dose” recommendations for the lower-strength product; the higher-strength product is not listed in the WHO table. Both products had been prequalified by WHO. The main concern with this combination is the toxicity of stavudine, although this problem is well defined. The Subcommittee noted the comments from the WHO Department of HIV that zidovudine-containing combinations are generally preferred.

The Subcommittee recommended that as the proposed combinations containing zidovudine exist and comply with WHO’s “ideal dose” requirements, they should be added to the EMLc. The quality of any individual product will have to be determined by regulatory review. The role of stavudine-containing combinations needs to be
considered. While they may well be essential at present during the scale-up process of antiretroviral treatment for children, their long-term usefulness is unclear. The Subcommittee therefore recommends that the combinations containing stavudine should be included on the EMLc, but reviewed again in the future. The Subcommittee also extensively discussed the roles of ritonavir-boosted lopinavir in paediatric HIV therapy and agreed that evolving safety data and the issue of how development influences the dose–plasma concentration–effect relationship for all medicines be considered in the determination of appropriate paediatric doses. In addition, the Subcommittee identified the need for heat-stable formulations of ritonavir-boosted protease inhibitors.

Section 6.5: Antiprotzoal medicines

Section 6.5.2: Antileishmaniasis medicines

**Liposomal amphotericin B (inclusion)**

The Subcommittee considered the application submitted by the WHO Department of Control of Neglected Tropical Diseases (NTD) for listing liposomal amphotericin B in the EMLc, for the treatment of visceral leishmaniasis. Expert reviews were prepared by Dr Shalini Sri Ranganathan (non-attending Temporary Adviser) and Dr Anita Zaidi.

The Subcommittee noted that the incidence of this infection is increasing in different parts of the world and that children account for a significant proportion of those with visceral leishmaniasis in disease-endemic areas. Morbidity and mortality related to this infection is substantial. Resistance to conventional therapy has been recorded, but there is inadequate information regarding the magnitude of this problem.

The available data, although not of good quality, suggest that liposomal amphotericin B is effective for the treatment of visceral leishmaniasis and is safe in children (39, 40). However, the Subcommittee is concerned that there are insufficient data to show how liposomal amphotericin B compares with the original formulation of this drug in terms of efficacy and safety in the treatment of visceral leishmaniasis. The Subcommittee noted that the different dosages and schedules tested have shown a good response and hence there could be flexibility in the dosage schedule. Several regimens have used a total dose of approximately 20 mg/kg and WHO recommends this dosage (41). The duration of in-patient therapy can vary, but is shorter than that with conventional therapies.

Safety data suggest that liposomal amphotericin B may be better than other therapies, but there is a paucity of good quality data on which to base conclusions.

The cost of therapy with liposomal amphotericin B can be significantly higher than that of conventional therapies. The Subcommittee was made aware of the preferential pricing offer which could help in addressing the issues of cost and availability associated with the procurement of liposomal amphotericin B in developing countries.
Section 8: Antineoplastic, immunosuppressives and medicines used in palliative care

At its meeting in 2007, the Subcommittee noted that access to cytotoxic medicines for children was an important public health issue and that a review of the cytotoxics listed and of the medicines for palliative care should be commissioned.

Section 8.2: Cytotoxic medicines (review)

The Subcommittee reviewed the documents received. Expert comments were provided by Professor Noël Cranswick and Professor Dai Yao Hua. Additional comments were made by Dr Ian Magrath, International Network for Cancer Treatment at Institut Pasteur, Brussels, Belgium, and Dr Judith Margolin, Baylor College of Pharmacy, USA.

The documents included a brief overview of sample protocols used for acute lymphoblastic leukaemia (ALL) and a review of the uses of methotrexate. No detailed evidence was provided concerning the efficacy, relevance or appropriate dosage of the medicines in children, the relative merit of one over the other, or any assessment of use within the developing world. Cytotoxic management of other common paediatric malignancies was also absent from the review. However, it was noted that oral dexamethasone is an essential component of the majority of paediatric oncological protocols, including ALL protocols of the United Kingdom, Children’s Oncology Group 1882 (North America), Berlin-Frankfurt-Munster and Hong Kong Special Administrative Region.

The review of methotrexate included a description of its use in the management of ALL and several studies were identified in which methotrexate was proven to be an effective therapy for ALL in children. Although intrathecal methotrexate forms part of standard care in the management of meningeal leukaemia and lymphomatous meningitis in children throughout the world, the evidence for efficacy in children for this indication included in the application was limited. Its use in other indications was also evaluated and the Subcommittee noted that side-effects of methotrexate may be significant and multiple. It was also noted that the evidence that the benefits of methotrexate outweigh the harms when used as an immune modulator in the management of conditions such as juvenile rheumatoid arthritis, uveitis,
inflammatory bowel disease, systemic lupus erythematosus (SLE), psoriasis and sarcoidosis was unclear.

The Subcommittee agreed that overall, the documents did not provide sufficient evidence to enable it to make an informed decision as to which cytotoxics should be included on the EMLc. A more extensive review of the relative merits of these treatment approaches is required, particularly with regard to the situation in developing countries. The comments from the INCTR suggested potential modifications to the EMLc that had already been made (e.g. deletion of levamisole and chlorimethine) and potential additions without any detailed assessment. They also note that certain cytotoxic medicines not included on the EMLc e.g. ifosfamide, mesna and hydroxyurea are used in the management of paediatric cancers (e.g. chronic myeloid leukaemia, lymphomas and sarcomas), whereas other drugs that are on the EMLc (e.g. fluorouracil) are rarely used in children.

An important question is the relevance of including cytotoxics on the WHO EMLc. On the one hand, countries that can afford to provide such care will develop protocols and formularies based on international standards, and presumably will have expertise available to administer the medicines appropriately. The relevance of the WHO EMLc to these countries may be limited. On the other hand, deletion of all medicines and an indication that countries should make their own judgement is likely to be a significant barrier to access in some countries, as well as providing no guidance to those countries wishing to start treatment programmes. The importance of treatment of HIV-related tumours in children, for example, is likely to increase and the availability of treatment is also likely to increase given donor priorities. In addition to the cost of treatment, most therapies are associated with significant side-effects requiring intensive support and monitoring, and contributing to high individual patient costs. Diagnostic precision is also important.

The Subcommittee considered how best to advance the provision of evidence-based information on selection and use of these medicines, including, potentially, the development of appropriate treatment guidelines so that it becomes a useful resource to countries. It was noted that this will require expanded consultation with experts and expert groups (e.g. the Children's Oncology Group) to determine the most common paediatric malignancies, the medicines used to treat them and the evidence (outcome-driven) suggesting their efficacy in improving both the quantity and quality of life.

It was therefore decided that the current list of cytotoxic medicines should remain unchanged at this stage.

Section 8.4: Medicines used in palliative care (inclusion)

The Subcommittee considered the review of medicines for palliative care commissioned by the Secretariat to ensure that appropriate medicines for the pharmacological management of the most prevalent and distressing symptoms in children with life-threatening and life-limiting conditions worldwide are included in
the EMLc. Expert comments were provided by Dr Robert Peterson and Dr Shalini Sri Ranganathan.

The Subcommittee noted that malignancy and HIV/AIDS were identified as the most common causes of childhood mortality appropriate to palliative care worldwide and that the 10 most frequent symptoms and symptom clusters (fatigue and weakness, pain, anorexia and weight loss, delirium and agitation, breathlessness, nausea and vomiting, constipation, depression, excess respiratory tract secretions and anxiety) had been identified based on available data.

The Subcommittee noted that the evidence to support efficacy and safety of medicines used in the management of these symptoms was generally weak and therefore, several recommendations in the proposal were based on experience from clinical practice. It also noted that several medicines proposed for addition to the EMLc were not listed in the International Drug Price Indicator Guide and availability worldwide can be an issue.

For some of the medicines identified in the proposal but already included in other sections of the EMLc, the Subcommittee was of the general opinion that the child-friendly dosage forms recommended need to be included in the EMLc. These are oral dexamethasone, oral liquid ibuprofen (for bone pain), a rectal solution form of diazepam and variable dosage forms of morphine. The Subcommittee acknowledged that availability of these dosage forms may be a problem in some parts of the world but considered that including them on the EMLc was one important way to promote improved availability and access.

To ensure appropriate first- and second-line management of nausea and vomiting due to different pathophysiological mechanisms, the proposal suggested that antiemetics with different mechanisms of action are required. The review proposed the following medicines: cyclizine (tablet: 50 mg; injection: 50 mg/ml), an antihistaminic antimuscarinic antiemetic that is effective for vomiting centre-mediated nausea and vomiting and levomepromazine (tablet: 25 mg; injection: 25 mg/ml) for chemoreceptor trigger zone-mediated nausea and vomiting. Although there is a lack of documented data on efficacy and safety, these two medicines are currently being used for this indication in some developed countries. Availability, especially of levomepromazine, may be a problem in many parts of the world. On balance, given that there is substantially more experience with the use of cyclizine, the Subcommittee recommended that it should be added to the EMLc in the dosage forms recommended specifically for use in palliative care.

The Subcommittee noted that the proposal recommends that laxatives are required for managing constipation, one of the most troublesome symptoms in palliative care. The options proposed were:

- docusate sodium (capsule: 100 mg; oral liquid: 50 mg/5 ml) as a faecal softening agent for use in children;
- senna (oral liquid 7.5 mg/5 ml) as a stimulant laxative.
The Subcommittee agreed that docusate sodium seems to be better tolerated and cheaper than lactulose, which is often the only available alternative, and therefore recommended its inclusion. The Subcommittee also noted that current clinical practice supports the use of a stimulant laxative, senna, in the management of opioid-induced constipation and hence the oral syrup was included in the EMLc for use in palliative care.

For the management of respiratory tract secretions, the proposal suggested that hyoscine hydrobromide may provide some benefit in terminal care. Despite the absence of data from large paediatric studies, the Subcommittee felt that the drug should be added to the EMLc. The Subcommittee particularly noted the potential usefulness of the patch presentation as an appropriate dosage form for use in children and decided, therefore to include the intravenous form and transdermal patch.

Midazolam is useful for managing anxiety and terminal agitation and delirium. The Subcommittee noted that there is insufficient evidence for the superiority of one benzodiazepine over another. However, the use of intravenous midazolam as a short-acting benzodiazepine is valuable, and the Subcommittee also noted that the intravenous form has been administered orally. It therefore recommended that midazolam should be included in the section on palliative care medicines for children.

Amitriptyline (10 mg tablet) is listed in the EML but was not endorsed for use in the treatment of depression in children at the meeting in 2007. The Subcommittee noted that this medicine is used in children for neuropathic pain and although there is, as for most other palliative care medicines in children, a lack of formal studies, it appears to be safe and effective. Hence the Subcommittee recommended that this medicine should be added to the EMLc specifically for use in palliative care.

The Subcommittee considered the general principle of whether medicines listed for palliative care should also have indications of age restrictions. On the one hand, it was noted that for several of the medicines added to the EMLc in this section evidence of efficacy and safety at all ages was not available. Specifically:

- cyclizine is not licensed for use in children under 6 years;
- docusate sodium is not licensed for use in children under 6 months;
- senna is not licensed for use in children under 2 years.

The Subcommittee considered that the licensed indications may not always reflect existing evidence, and also noted the importance of access to these products for children in need of palliative care, and therefore decided not to indicate age restrictions on the use of these products for this purpose.
Section 12: Cardiovascular medicines

Quinidine (review)

_Complementary List_

The Subcommittee considered the review of quinidine that proposed its deletion from the EMLc. At its meeting in 2007, the Subcommittee identified antiarrhythmics as a class of medicines for which further information was required before any could be endorsed as essential in children. Expert comments were provided by Dr Helena L. Coelho and Professor Noël Cranswick.

The Subcommittee noted that there was a paucity of data on the need for, and use of, antiarrhythmics in children generally, but acknowledged that the effects of quinidine are likely to be similar to those observed in adults. In adults, there is good evidence to show that quinidine suppresses atrial fibrillation (42). However, there is also high quality evidence to show that use of this medicine is associated with higher rates of potentially fatal adverse events such as Torsade de Pointes (43) and that mortality is higher in those who use this medicine than in controls. Adverse events can even occur at therapeutic and sub-therapeutic serum levels and occasionally without marked prolongation of the QT interval. There is also the possibility of dangerous interactions of the drug with commonly used medicines.

Regulatory authorities have not approved this medicine for paediatric use. In the absence of evidence to establish public health need and efficacy and safety, the Subcommittee recommended that quinidine not be included in the EMLc.

Rheumatic fever and rheumatic heart disease (review)

The Subcommittee considered the review of antibiotics for the prevention and treatment of rheumatic fever and rheumatic heart disease in children, commissioned to determine whether the antibiotics currently listed are appropriate and adequate.

The Subcommittee noted that the burden due to rheumatic fever and rheumatic heart disease is high, especially among children in less developed countries. Antibiotics are proven to be effective in primary prevention, treatment of acute rheumatic fever and for secondary prophylaxis.

For all three situations, benzathine benzyl penicillin is recommended as the first-line therapy (44). Evidence shows that this antibiotic can reduce recurrences and that IM therapy is better than oral therapy for this outcome (45). However, oral phenoxymethyl penicillin is an alternative if injections are unacceptable or not possible. In patients with hypersensitivity to penicillins, erythromycin is the recommended antibiotic. These three antibiotics are listed in the current EMLc.

The Subcommittee recommended that the antibiotics listed currently in the EMLc (as shown below) are adequate for the prevention and treatment of rheumatic fever and rheumatic heart disease:
— benzathine benzyl penicillin: powder for injection: 900 mg (= 1.2 million IU) in 5-ml vial; 1.44 g (= 2.4 million IU) in 5-ml vial.

— phenoxyethyl penicillin: powder for oral liquid: 250 mg (as potassium salt) in 5 ml; tablet: 250 mg (as potassium salt).

— erythromycin: capsule or tablet: 250 mg (as stearate or ethyl succinate); powder for oral liquid: 125 mg (as stearate or ethyl succinate).

Section 13: Dermatological medicines (topical)

Dermatological medicines (review)

The Subcommittee considered the review of dermatological medicines prepared by the International League of Dermatological Societies (ILDS). Expert comments were provided by Dr Shalini Sri Ranganathan and Professor Harshi Sachdev. Additional comments were provided by Médecins Sans Frontières.

Diseases of the skin are common in children and are among the leading reasons for visits to primary health care services (46). Several different topical and systemic medicines are required to treat the varied conditions affecting the skin. The Subcommittee noted that the review identified 10 diseases as priorities and that recommendations for addition and deletion were made in addition to retaining most of the medicines already in the EMLc.

The Subcommittee noted that the review by the ILDS recommends that the following medicines are retained:

— miconazole and Whitfield’s ointment (benzoic acid + salicylic acid) (Section 13.1);
— silver sulfadiazine 1% cream, gentian violet 0.5% in alcohol or water and potassium permanganate 1/10 000 aqueous solution (Section 13.2);
— 1% hydrocortisone cream and 0.1% betamethasone cream and calamine lotion (Section 13.3);
— Salicylic acid preparations, benzoyl peroxide 5% cream or lotion and urea 5% or 10% cream or ointment (Section 13.5);
— 10–25% benzyl benzoate, permethrin cream/solution (Section 13.6).

Povidone iodine 10% solution and chlorhexidine solution listed in Section 15.1, are also useful for topical treatment of skin diseases.
Cloxacillin, amoxicillin, erythromycin, doxycycline, benzyl penicillin, griseofulvin, aciclovir, chlorphenamine, cefalexin and ivermectin are also required for managing skin diseases resulting from infectious causes and are listed in other sections of the EMLc.

The Subcommittee noted that the review recommended the addition of the following medicines – econazole cream (13.1); tetracycline 3% ointment (13.2); lindane cream/lotion (13.6); crotamiton ointment (13.6); petrolatum and oral terbinafine.

As miconazole ointment or cream is listed in the EMLc with a square box, addition of econazone is not required.

Although topical tetracycline may be useful for certain skin conditions, there are insufficient clinical data on its efficacy and safety in children to determine whether it should be listed. The Subcommittee noted the recommendation that neomycin sulfate + bacitracin ointment (13.2) be deleted from the EMLc. Information from the review suggested that neomycin + bacitracin is associated with allergic manifestations and better topical applications are currently available. The Subcommittee concluded that insufficient information is currently available and proposed a review of the comparative effectiveness and safety of common antibiotics for the treatment of skin infections in neonates, particularly pyoderma and omphalitis.

The Subcommittee noted that resistance to first-line scabicides and pediculocides has appeared, so there is a need for alternative therapy. However, it was concerned about the safety profile of lindane and in the absence of a more detailed assessment of its safety, decided not to include it on the EMLc at this time. While crotamiton appears to be safe in children, data to support its effectiveness in comparison with permethrin were not provided and would need to be considered before it could be added to the EMLc.

The Subcommittee felt that there was insufficient evidence to determine that petrolatum met the criteria of an essential medicine and hence it was not included on the EMLc.

There is evidence that oral terbinafine is useful in treating tinea capitis, commonly seen in children. The Subcommittee reconsidered the prior review of oral antifungals in children (2007) and concluded that there was an insufficient basis for including oral terbinafine on the EMLc at that time.

The Subcommittee noted the recommendation that dithranol preparation (13.5) be deleted from the EMLc given its caustic potential. This recommendation was accepted.
Section 15: Disinfectants and antiseptics

Chlorhexidine (new formulation)

The Subcommittee considered the application to include 4% chlorhexidine in the EMLc for topical cord care in settings where risk of umbilical cord infections is high. Expert comments were provided by Drs Jacqueline Deen and Gregory Kearns.

The Subcommittee noted that the risk of umbilical cord infections is higher in areas where neonatal mortality rates are already very high and that these infections contribute significantly to neonatal mortality. Cord infection rates are higher in areas where home delivery rates are high, where clean delivery is not universally guaranteed and where traditional practices of cord care increase the risk of infection. There is a general consensus that in unclean deliveries, topical antiseptics for cord care may be of use in preventing infections.

Systematic reviews do not show superiority of any one antiseptic. However, a recent large community-based cluster randomized trial in Nepal (47), showed that chlorhexidine 4% reduces incidence of omphalitis as compared to dry care. A reduction in neonatal mortality was also observed when treatment was started within 24 hours of birth. Another recent trial in Italy (48) failed to confirm these findings. One possible explanation for the discrepancy in the trial results is the different standards of perinatal care in the two countries.

Chlorhexidine is currently listed in the EMLc, with a square box, as solution 5% (digluconate) for dilution, in Section 15.1 (antiseptics). The Subcommittee noted that for the randomized controlled trial which showed benefit, the chlorhexidine 4% was prepared for use by diluting a 20% commercially available solution (47). The options are therefore to add a 20% solution of chlorhexidine digluconate and specify it for dilution or add 7.1% as proposed in the application. In the absence of a commercially available 7.1% solution, the Subcommittee decided to include a 20% solution as digluconate on the EMLc, specifying the dilution required in the proposed WHO Model Formulary for Children.

Section 17: Gastrointestinal medicines

Pancreatic enzymes (inclusion)

The Subcommittee reviewed the application for the inclusion of pancreatic enzymes on the EMLc, for the management of severe pancreatic insufficiency. Expert comments were provided by Professor Harshi Sachdev and Dr Elizabeta Zisovska.

The Subcommittee noted that the majority of paediatric patients with pancreatic insufficiency suffer from cystic fibrosis, although several other conditions (e.g. chronic pancreatitis and post-gastric surgery) may also contribute to this condition. It was acknowledged that cystic fibrosis occurs worldwide, and that pancreatic insufficiency may be present in up to 90% of these patients. The resulting malnutrition may lead to a multitude of negative clinical outcomes, including lower
life expectancy, poor growth, increased susceptibility to infections, and deterioration in lung function.

The Subcommittee noted that the application cited several good quality randomized trials, which appeared to support the use of pancreatic enzymes for treatment of pancreatic insufficiency in cystic fibrosis. A significant difference in mean protein and fat absorption was seen when comparing placebo to pancreatic enzyme replacement therapy; however the aim of the majority of studies was to evaluate different doses and formulations. Two randomized controlled studies (49, 50) carried out by the manufacturer of Creon, Solvay, were described, where a co-efficient of fat absorption (CFA) of up to 89.1% following Creon treatment was observed. Similar efficacy was demonstrated between different preparations included in the application.

Limited studies involving the use of pancreatic enzyme therapy in the management of conditions other than cystic fibrosis were included in the application, and the Subcommittee noted that evidence for safety and efficacy in infants younger than six months was limited.

It was the conclusion of the Subcommittee that sufficient evidence exists for the efficacy and safety of pancreatic enzyme replacement therapy in children, with resulting improvement in morbidity and mortality of patients with severe pancreatic insufficiency. Given the need for the dose to be monitored and titrated according to clinical response, it was agreed that pancreatic enzymes should be included on the Complementary list.

Further discussion by the Subcommittee focused on the recent warnings about phthalates in the formulations and their potential safety implications.

Section 17.2: Antiemetic medicines (review)

At its 2007 meeting, the Subcommittee requested a review of the choice of antiemetics for inclusion on the EMLc. The Secretariat commissioned a review, considered below. It was noted that antiemetic medications are not currently included in any of the major guidelines (American Academy of Pediatrics, CDC or WHO) for use in children with acute gastroenteritis. Expert comments were provided by Professor Prakash Mohan Jeena.

The commissioned review included a number of systematic reviews evaluating the effectiveness of antiemetics in the management of acute gastroenteritis in children. It was noted that although the studies demonstrated ondansetron to be significantly superior to placebo in preventing vomiting, none of the studies supported the routine use of antiemetic medications in the management of acute gastroenteritis in children. The Subcommittee also noted that the majority of studies reported a significant increase in side-effects associated with the use of antiemetics.

Overall there was insufficient evidence to support the routine use of antiemetic medications in the management of children with gastroenteritis, and potentially a high risk of associated adverse events, negating any significant benefit to children.
However, the Subcommittee noted that antiemetic medicines were important in the context of post-operative nausea and vomiting as well as in conjunction with chemotherapy. It therefore recommended that before deleting the existing medicines, a further assessment of this class of drugs in post-operative patients and those receiving cancer chemotherapy, should be carried out, especially with regard to newer products, such as 5-HT3 antagonists.

Section 18: Hormones, other endocrine medicines and contraceptives

Hydrocortisone and fludrocortisone (inclusion)

The Subcommittee considered the application for the inclusion of the adrenal hormones fludrocortisone and hydrocortisone to the EMLc. Expert comments were provided by Dr Stuart Macleod and Professor Tony Nunn. Numerous external comments in support of the proposal were received from health professionals, associations and individuals.

The Subcommittee noted that hydrocortisone and fludrocortisone are used in the management of primary and secondary aldosterone deficiency caused by congenital adrenal hyperplasia and Addison disease, that both medications are licensed for use in all ages, and that treatment should be of lifelong duration. It was noted that fludrocortisone is currently the only mineralocorticoid available for aldosterone replacement in congenital adrenal hyperplasia, and that consequently there are no comparative efficacy or safety studies for the management of mineralocorticoid deficiency in congenital adrenal hyperplasia.

The application identified a retrospective study of 484 patients from five European countries, which demonstrated a decrease in mortality rate from 11.9% in untreated patients to 4.3% in those patients who were treated with fludrocortisones (51).

Only one small study (52) of nine patients comparing hydrocortisone with prednisone for the management of congenital adrenal hyperplasia was included in the application. It showed that prednisolone had significantly greater adverse effects on growth than hydrocortisone. It was acknowledged however that the use of other glucocorticoids such as dexamethasone and prednisolone is generally avoided in children due to adverse effects on growth.

The Subcommittee agreed that fludrocortisone and hydrocortisone are both essential medicines for the management of congenital adrenal hyperplasia and adrenal insufficiency in children, and included them on the EMLc.

Section 24: Psychotherapeutic medicines (review)

At its meeting in July 2007, the Subcommittee requested a review of the section on psychotherapeutic medicines to determine what was essential in addition to the products considered at that meeting. In particular the sections on anxiety and sleep disorders, obsessive-compulsive disorders and panic attacks, and substance abuse were highlighted as
needing further review. The Secretariat commissioned a review, published for discussion at the meeting. Expert comments were provided by Dr Kalle Hoppu and the WHO Department of Mental Health and Substance Abuse.

The Subcommittee decided that the review is best considered as a preliminary overview; as has been pointed out by the WHO Department of Mental Health and Substance Abuse, there is a need for more detailed summaries of evidence to be prepared before the suggested additions of medicines to the EMLc could be supported. It was difficult to support addition of any new medicines on the basis of the information presented.

The Subcommittee recommended that a review be undertaken by the Secretariat to identify the most common mental health disorders in children that require medication and that this information should be used as the basis for further development of this section of the EMLc. The Subcommittee recommended retaining chlorpromazine and haloperidol at present but recognized that their patterns of use support inclusion on the Complementary List. There was no change to the listing of fluoxetine.

**Section 25: Medicines acting on the respiratory tract**

**Salbutamol (review)**

Oral salbutamol is currently included on the list in liquid and tablet formulation. In July 2007, the Subcommittee noted that these formulations are rarely used in the management of childhood asthma in many countries and requested a review of the evidence for the use of these forms, with particular emphasis on young children with viral-related wheeze. A review was subsequently received by the Secretariat. Expert comments were provided by Professor Noël Cranswick and Mr Andy Gray.

Given the superiority of inhaled salbutamol over oral salbutamol for the management of asthma, the lack of evidence for the use of bronchodilators in bronchiolitis, and the paucity of evidence for the use of oral salbutamol in children with viral wheeze, the Subcommittee agreed that at present, oral salbutamol should only be considered for use when treatment with inhaled asthma medications is not feasible. The EMLc was annotated to reflect this recommendation.

**Surfactant (inclusion)**

The Subcommittee reviewed the application for the inclusion of surfactant on the EMLc for the prophylaxis and management of primary respiratory distress syndrome in preterm infants, and secondary surfactant deficiency in infants. Expert comments were provided by Professor Noël Cranswick and Dr Elizabeta Zisovska.

High quality evidence demonstrating that both prophylactic and rescue surfactant improve clinical outcome in premature neonates was identified in the application. This included a Cochrane systematic review (53) of seven randomized controlled trials in which clinical outcomes were assessed following prophylactic administration of synthetic surfactant to premature infants aged between 25 to 34 weeks gestation, and with birth weights between 500 and 1350 grams. The meta-analysis showed a
statistically significant decrease in the risk of pneumothorax, a decrease in the risk of pulmonary interstitial emphysema, and a decrease in risk of neonatal mortality. However an increased risk of developing patent ductus arteriosus and pulmonary haemorrhage was demonstrated.

The Subcommittee noted that the European Consensus Guidelines recommend the use of natural over synthetic surfactant as a prophylactic approach in infants of less than 27 weeks gestation, and for those between 26 and 30 weeks gestation if intubation is required in the delivery room or if no prenatal corticosteroids have been received. The American Academy of Pediatrics guidelines suggest that surfactant should be given to infants with respiratory distress syndrome as soon as possible after intubation, regardless of gestational age or exposure to prenatal corticosteroids.

A systematic review (54) which included 11 trials showed that although the use of natural rather than synthetic surfactant resulted in a significant reduction in the risk of pneumothorax and mortality, there was a trend towards an increase in overall intraventricular haemorrhage following the use of natural surfactant.

The Subcommittee noted that limited evidence is available to determine the optimal method of surfactant administration and that high-quality evidence is lacking for the use of surfactant in other conditions such as persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, neonatal pulmonary haemorrhage and meconium aspiration syndrome.

Despite evidence for an increased risk of patent ductus arteriosus, pulmonary haemorrhage and intraventricular haemorrhage following treatment with surfactant therapy, the benefits of use in management of respiratory distress syndrome in the neonatal population clearly outweigh the risks. Costs of surfactant were noted to be high. The Subcommittee concluded that the application had identified high quality evidence for the use of surfactant in the management of respiratory distress syndrome in premature infants. It was added to the EMLc and placed in a new section devoted to neonatal medicines and categorized as a Complementary medicine given the nature of its use.

**Section 27: Vitamins and minerals**

**Retinol**

The WHO Department of Child and Adolescent Health and Development commissioned a review of the evidence of potential benefit of prophylactic/routine administration of vitamin A to neonates and infants younger than six months, with a view to updating the current recommendations about its use. The proposal to delete the 50 000 IU formulation currently on the EMLc arose from the results of the review. Expert comments were provided by Dr Stuart Macleod and Dr Robert Petersen.

The two reports, (55) provided as confidential drafts to the Subcommittee, were the manuscript version of the systematic review of neonatal vitamin A supplementation (56) and the report to WHO on the benefits and safety of vitamin A supplementation in the first six
months of life (57). Both are comprehensive systematic reviews and both found that the existing evidence shows no benefit of routine supplementation in terms of mortality or morbidity in these age groups. The Subcommittee noted that administration of this drug to young infants has been associated with an increased occurrence of bulging fontanelle.

Five additional Cochrane reviews were identified examining administration of vitamin A to other subgroups of children: low birth weight infants, children with cystic fibrosis, children with measles, for prevention of lower respiratory tract infections, and non measles pneumonia in children under seven years of age (58, 59, 60, 61, 62).

In low-birth-weight children, most studies reported use of intramuscular vitamin A. There was a trend towards benefit in terms of survival and reduced oxygen requirement, but most of the outcomes analysed were not statistically significant. No studies were identified in the review of cystic fibrosis. In the review of treatment of measles, vitamin A was administered at doses of 100 000 or 200 000 IU and was found to reduce mortality. The reviews of non-measles pneumonia and lower respiratory tract infections found no evidence of benefit of vitamin A supplementation in children under seven years of age.

The Subcommittee considered that there was no clear need for a 50 000 IU oral dose for routine prophylaxis against vitamin A deficiency during the first six months of life. The 50 000 IU dosage form is also not appropriate for routine supplementation in children over six months of age for whom the recommended dose is 100 000 or 200 000 IU. Therefore the only potential use for the low-dose capsule would be for the outpatient treatment of clinically proven vitamin A deficiency in neonates and infants under six months of age; a condition that is exceedingly rare. The Subcommittee recommended that the 50 000 IU dosage form be deleted from the EMLc.

**New Section 28: Ear, nose and throat conditions in children**

The Subcommittee considered the review which was commissioned to identify essential medicines for the treatment of ear, nose and throat conditions in children. Expert comments were provided by Dr Kalle Hoppu and Professor Prakash Mohan Jeena.

Based primarily on South African guidelines and WHO guidelines for treating ear, nose and throat conditions in children, the priority conditions identified were acute croup, epiglottitis, epistaxis, otitis externa, otitis media (acute and chronic), rhinosinusitis and sore throat. The Subcommittee noted that many medicines required for treating these conditions were already listed. However, several more needed to be considered for addition. These included preparations for both topical and systemic use. There was a lack of documented evidence for the efficacy and safety of most of the medicines that needed to be considered for addition. Most available data came from studies in adults or from those involving both adults and children. However, these medicines are recommended in widely accepted guidelines.

The Subcommittee noted that there is evidence to show that antibiotic ear drops are of benefit in the treatment of otitis externa. There is evidence to suggest that quinolone ear drops are superior to other otic antimicrobial formulations. The Subcommittee considered the importance of the available information regarding combination antimicrobial agent—
corticosteroid formulations for the treatment of otitis externa (63) and found no compelling evidence to support the inclusion of combination products.

The Subcommittee therefore recommended that acetic acid ear drops and ciprofloxacin ear drops be added to the EMLc, the ciprofloxacin ear drops with a square box annotation.

The Subcommittee decided that based on available evidence, the inclusion of a nasal corticosteroid could be recommended. Further, the Subcommittee recommended the inclusion of a decongestant nasal spray/nose drops, listing xylometazoline with a square box annotation. Topical ephedrine was not included in recognition of its potential for abuse.

The Subcommittee requested a full proposal for a non-sedating antihistamine.

**New Section 29: Essential medicines for neonates**

The Subcommittee reviewed the application for inclusion of a separate section for essential medicines for neonates. In October 2007, the Expert Committee recommended that:

1. The Subcommittee should consider whether it would be appropriate to develop a separate section of the EMLc for neonates.
2. If a separate section is recommended, should it be retained for the “master list? and
3. How should work in this neglected area be proritized?

The Secretariat prepared the review that was considered by the Subcommittee. Expert comments were provided by Professor Noël Cranswick and Dr Gregory Kearns. The general issues noted were:

— There was a paucity of high quality evidence for the use of medications in the neonatal period and the subsequent off-label and unlicensed use in this population are major problems.

— A more detailed and systematic review of the available evidence for efficacy and safety of the medicines recommended for neonates may be required.

— Medicines were categorized as recommended essential medicines for neonates, missing essential medicines for neonates, medicines requiring further review before a recommendation for use in neonates can be made, and medicines not recommended for neonates.

The Subcommittee noted that the medicines currently missing from the EMLc, and recommended exclusively for use in neonates were:

— *Intravenous ibuprofen or indomethacin* – injectable non-steroidal anti-inflammatory medicines for use in the management of patent ductus arteriosus in preterm infants. It was noted that there is evidence that ibuprofen and indomethacin are equivalent in efficacy for this indication (64). This meta-analysis, not included in the application, of 11 trials comparing the treatments for management of patent ductus arteriosus in the preterm infant, showed that ibuprofen was as effective as indomethacin in closing the
patent ductus arteriosus. No significant differences were found in the incidence of complications, except that there was less renal impairment associated with ibuprofen.

- Prostaglandin E1 or E2 injection – used to maintain patency of the ductus arteriosus when a cyanotic lesion or interrupted aortic arch presents in a newborn. No systematic reviews of the efficacy of prostaglandin in the management of patent ductus arteriosus were identified, but this therapy is recommended in most clinical treatment guidelines.

- Surfactant – See Section 25 – Medicines acting on the respiratory tract.

Given that the review by the Secretariat identified only four medicines for exclusive use during the neonatal period, the Subcommittee recommended inclusion of a new section for these specific medicines. The medicines were:

- caffeine citrate, already included under Section 25;
- ibuprofen injection, to be included in this new section of the EMLc, with a square box to indicate that indomethacin may be an appropriate alternative;
- prostaglandin E1 or E2 injection;
- surfactant (see Section 25).

Given that caffeine citrate is recommended for use in health facilities generally and does not need to be administered in an intensive care unit, it was considered that it should remain on the Core List. The other medicines were included on the Complementary List.

The Subcommittee then considered additional aspects of the use of other medicines, already on the EMLc, in neonates. Comments were received from the WHO Child and Adolescent Health and Development Department, which questioned the need to include chloramphenicol, vitamin A, zinc sulfate and aciclovir 3% for neonates.

There is no evidence for the efficacy of oral zinc in children under six months of age. A recent review from the Cochrane Collaboration identified 18 randomized controlled trials that compared zinc with placebo in young children. This included two large trials that were conducted in children aged less than six months with acute diarrhoea, and showed no evidence of an effect on any of the outcomes (65).

Evidence for the efficacy of chloramphenicol specifically in the neonatal population is limited. A Cochrane review showed equivalent efficacy of ceftriaxone or cefotaxime with conventional antibiotics (including chloramphenicol) when given for the management of acute bacterial meningitis (66).

Neonates with suspected herpes simplex virus infection, including those with skin, eye or mouth disease, should be treated with intravenous aciclovir. There is no evidence for the efficacy of topical aciclovir in the management of neonatal herpes infections.

On the basis of the review, medicines on the EMLc used in neonatal care were identified and are included in Annex 6 to this report. The Subcommittee considered that a separate list of
medicines for neonates could cause unnecessary confusion and that an annex listing medicines that can be safely used in neonates was the best option at the present time.

5. Summary of recommendations

Section 4: Antidotes and other substances used in poisonings

4.2 Specific

— NAC oral solution added.

Section 6: Anti-infective medicines

6.2.1 Beta-lactam medicines

— cefalexin – capsule, tablet and powder for dilution added.
— cefotaxime – added to Complementary List for use in hospitalized neonates.
— ceftazidime – request for review removed.
— ceftriaxone – insertion of note to restrict use to infants older than 41 weeks corrected gestational age; note added regarding avoidance of use in administration with calcium and in infants with hyperbilirubinaemia; request for review removed.
— imipenem–cilastin – note added stating that meropenem is indicated for the treatment of meningitis in children over the age of 3 months; request for review removed.
— procaine benzylpenicillin – age restriction removed; note added that it is not recommended as first-line treatment for sepsis and/or meningitis; request for review removed.

6.2.2 Other antibacterials

— azithromycin – age restriction removed.
— ciprofloxacin – removal of note stating that it is for use only in Shigella infections; IV and oral liquid formulation added; request for review removed.
— doxycycline – age restriction added limiting use to children over 8 years of age with non-life threatening conditions; removal of note regarding use only in treatment of cholera; request for review removed; 50-mg tablet and oral liquid added.
— erythromycin – intravenous formulation deleted; request for review removed.
— gentamicin – request for review removed.
— sulfadiazine – intravenous form deleted; oral form moved from Section 6.2.2 to Section 6.5.4.

6.2.4 Antituberculosis medicines

— Deletion of fixed-dose combination antituberculosis medications (rifampicin + isoniazid, rifampicin + isoniazid + pyrazinamide).
6.4.2.3 Protease inhibitors
   — Addition of new doses of fixed-dose combination tablets for antiretroviral medicines.

6.5.2 Antileishmaniasis medicines
   — Liposomal amphotericin B added to the Core List of antileishmaniasis medicines.

Section 8: Antineoplastic, immunosuppressives and medicines used in palliative care

8.4 Medicines used in palliative care
   — Ten new medicines added (amitriptyline, cyclizine, dexamethasone, diazepam, docusate sodium, hyoscine hydrobromide, ibuprofen, midazolam, morphine and senna).

Section 10: Medicines affecting the blood

10.2 Medicines affecting coagulation
   — Heparin sodium strength 20 000 IU deleted.

Section 12: Cardiovascular medicines

12.5 Antithrombotic medicines
   — Antithrombotic medicines section deleted.

Section 13: Dermatological medicines (topical)

13.5 Medicines affecting skin differentiation and proliferation
   — Dithranol preparation deleted.

Section 15: Disinfectants and antiseptics

15.1 Antiseptics
   — 20% chlorhexidine digluconate solution added.

Section 16: Diuretics not mentioned in text

   — Spironolactone – strength changed to 5 mg/5 ml; 10 mg/5 ml; 25 mg/5 ml (previously 1–20 mg/ml).

Section 17: Gastrointestinal medicines

   — Pancreatic enzymes added to the Complementary list.
Section 18: Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes
   — Fludrocortisone and hydrocortisone added to the List.

18.5 Insulins and other antidiabetic agents
   Insulin injection strength 40 IU/ml deleted.

Section 24: Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders
   — Chlorpromazine and haloperidol moved to the Complementary list.

Section 25: Medicines acting on the respiratory tract

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease
   — Oral salbutamol – note added that treatment should only be considered when inhaled asthma therapy is not feasible.

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

26.2 Parenteral
   — Glucose (4%) with sodium chloride (0.18%) deleted.
   — Potassium chloride strength 7.5% and 15% added, 11.2% deleted.

Section 27: Vitamins and minerals
   — Retinol – 50 000 IU dosage form of vitamin A deleted.

Section 28: Ear, nose and throat conditions in children
   — New ear, nose and throat section created.
   — Acetic acid drops, budesonide, ciprofloxacin drops and xylometazoline spray added.

Section 29: Essential medicines for neonates
   — New section created for specific medicines in neonatal care.
   — Caffeine citrate moved to this section from Section 25.2.
   — Surfactant, prostaglandins and intravenous ibuprofen added.
   — Medicines used in neonatal care identified and included in Annex 6.
Table 1. Age restriction table

— New additions – ceftriaxone, xylometazoline.
— New deletions – azithromycin, clindamycin, procaine benzylpenicillin.

Summary of new reviews/applications requested during the meeting of the Subcommittee:

— Appropriate medicines for use in resuscitation in children.
— Essential medicines for management of neuropathic pain in children, including the role of lamotrigine, amitriptyline and gabapentin.
— Review of liposomal amphotericin B as a treatment for fungal infections in children.
— Antimonials as essential medicines for leishmaniasis, and whether they should be on the Core or Complementary list.
— Safety and efficacy of streptomycin in childhood tuberculosis.
— Review of safety of topical antibiotics, including tetracycline ointment in neonates.
— Clinical use of ondansetron in children.
— The role of leukotriene antagonists in the management of childhood allergic rhinitis.
— Application for heat-stable protease inhibitors for management of HIV.
— Comparison of sulfadiazine and co-trimoxazole in the treatment of toxoplasmosis.
— Application for glucagon.
— Development of child-friendly equipment for medicine administration for all ages.
— Review of use of methylene blue in children.
— Review of use of oral iron/lead chelators in children.
— Assessment of two new clinical trials on safety and efficacy of procaine benzylpenicillin in neonates.
References of the Second Report of the Subcommittee


(30) Rao SC et al. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database of Systematic Reviews, 2006, Issue 1. Art. No.: CD005091.


(56) Gogia S, Sachdev H. Neonatal vitamin A supplementation for the prevention of mortality and morbidity in infancy: systematic review of randomized controlled trials 2008. New Delhi, Department of Paediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research. (Manuscript under review for publication).

(57) Gogia S, Sachdev H. Benefits and safety of vitamin A supplementation in the first half of infancy: systematic reviews of randomized controlled trials. (Unpublished draft submitted to the World Health Organization.)


Appendix A: Declaration of interests of Subcommittee members

The members of the Subcommittee reported the following:

Professor Noël Cranswick reported being an investigator on trials for GlaxoSmithKline, Quintiles, Novartis, Uriach, Biomarin and Biota but not for any products or related products to those being considered at the meeting, and also reported holding shares in Biota through a family trust.

Mr Andy Gray reported having accepted travel support and honoraria from AstraZeneca, Aspen Pharmacare for continuing professional development lectures and being a study pharmacist for the International Clinical Trials Unit and Center for the AIDS Programme of Research in South Africa in KwaZulu-Natal. He also reported being a director of a government funding agency for biotechnology, and being a member of the Scheduling and Naming Committee of the Medicines Control Council of South Africa.

Dr Kalle Hoppu reported receiving lecture fees from Norit Pharmaceuticals Netherlands, Leiras Ltd. Finland (2005) and Oy Swedish Orphan Ab Finland (2008). Dr Hoppu reported providing consultation advice once to Lundbeck A/S Denmark, provided through the Clinical Research Institute Helsinki University Central Hospital Ltd/Finnish Investigators Network for Paediatric Medicines.

Dr Gregory Kearns reported providing consultancy services for Abbott, Biodelivery Sciences, Santarus, Mead Johnson, Wyeth Pharmaceuticals, Cubist Pharmaceuticals, Schwarz Pharma, Proctor and Gamble, Orexigen, Tyco Healthcare, Altana Pharma and Centocor. In addition, Dr Kearns reported that his employer holds research contracts related to child health with the private sector. He also serves as a member of the US Food and Drug Administration Clinical Pharmacology Advisory Committee, and provides consultation to the National Institutes of Health regarding paediatric drug development.

Professor Prakash Mohan Jeena declared being a principal investigator on a trial of protease inhibitors in HIV (GlaxoSmithKline) and receiving travel support and honoraria for lectures from GlaxoSmithKline, Wyeth and Sanofi-Pasteur. He also chaired the essential drugs programme for children in South Africa.

Dr Anita Zaidi reported that her department received research funding from Wyeth Pharmaceuticals and GlaxoSmithKline for work on vaccines.

Dr Peter Kazembe reported that his employing institution received some funding from The Abbot Fund, through Baylor College of Medicine, USA.

Mrs Jehan Mohammed Ali Al-Fannah and Dr Helena L. Coelho and reported no conflict of interest.
The Temporary Advisers reported the following:

Dr Stuart Macleod reported serving as Executive Director of the Child and Family Research Institute, Vancouver, and as Associate Dean (Research) University of British Columbia. Both institutions hold child health research contracts with the private sector, but he is not principal investigator on any of these contracts. He has also provided consultation and has served on advisory committees for federal and provincial governments in Canada.

Dr Robert Peterson reported receiving travel expenses to attend the Board meetings of the Institute for Regulatory Science, Centre for Medicines Research International, and also for being a member of the Expert Drug Advisory Committee of the Canadian Agency for Drug and Health Technology Assessment.

Professor H. P. S. Sachdev reported receiving honoraria for speaking at the National Probiotic Symposium (India, 2007) and the National Indian Academy of Paediatrics Conference (2007) on the use of probiotics and zinc to treat diarrhoea. He has also served on policy committees established by the Government of India.

Professor Anthony Nunn provided advice to the European Medicines Agency and the UK Government Commission on Human Medicines. He receives research support for the study of medicines in children from the UK National Institute of Health Research.

Dr Jacqueline Deen served as a paid consultant to GlaxoSmithKline to develop a training module until May 2008. Her employer, the International Vaccine Institute receives funding from the Bill and Melinda Gates Foundation, other foundations and vaccine producers. Dr Deen is currently an investigator in a malaria trial being conducted in Africa and funded by the Wellcome Trust.

Professor Dai Yao Hua and Dr Elizabeta Zisovska reported no conflict of interest.

Dr Shalini Sri Ranganathan was a non-attending Temporary Adviser who reported no conflict of interest.

For the purposes of this declaration, the participants noted that many of them worked in departments that received funding from other commercial entities but they were not directly involved in these projects. Several participants have held positions in academic or learned societies that have provided general direction on matters pertinent to child health.
**Appendix B: Essential medicines that can be used in neonates**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CORE</strong></td>
<td></td>
</tr>
<tr>
<td>oxygen</td>
<td>Inhalation (medicinal gas) (<em>Section 1.1</em>)</td>
</tr>
<tr>
<td>lidocaine</td>
<td>Injectable solution: 1%; 2% (hydrochloride) in vial</td>
</tr>
<tr>
<td></td>
<td>Topical forms: 2% to 4% (hydrochloride) (<em>Section 1.2</em>)</td>
</tr>
<tr>
<td>diazepam*</td>
<td>Injection: 5 mg/ml in 2-ml ampoule (<em>Section 1.3</em>)</td>
</tr>
<tr>
<td></td>
<td>* Preparations without benzyl alcohol should be used for neonates.</td>
</tr>
<tr>
<td>morphine</td>
<td>Injection: 10 mg (as morphine hydrochloride or morphine sulfate) in 1-ml ampoule (<em>Sections 1.3 and 2.2</em>)</td>
</tr>
<tr>
<td></td>
<td>Oral liquid: 10 mg (as morphine hydrochloride or morphine sulfate)/5 ml (<em>Section 2.2</em>)</td>
</tr>
<tr>
<td>paracetamol</td>
<td>Oral liquid: 125 mg/5 ml</td>
</tr>
<tr>
<td></td>
<td>Suppository: 60 mg (<em>Section 2.1</em>)</td>
</tr>
<tr>
<td>epinephrine</td>
<td>Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1 ml ampoule (<em>Sections 3 and 25.1</em>)</td>
</tr>
<tr>
<td>calcium gluconate</td>
<td>Injection: 100 mg/ml in 10-ml ampoule (<em>Section 4.2</em>)</td>
</tr>
<tr>
<td>naloxone</td>
<td>Injection: 400 micrograms (as hydrochloride) in 1-ml ampoule (<em>Section 4.2</em>)</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>Injection: 200 mg/ml (phenobarbital sodium) (<em>Section 5</em>)</td>
</tr>
<tr>
<td>phentoytin</td>
<td>Injection: 50 mg/ml in 5-ml ampoule (as sodium salt)</td>
</tr>
<tr>
<td></td>
<td>Oral liquid suspension: 25 mg to 30 mg/5 ml (<em>Section 5</em>)</td>
</tr>
<tr>
<td>amoxicillin as trihydrate (as sodium salt)</td>
<td>Powder for oral liquid: 125 mg (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml (<em>Section 6.2.1</em>)</td>
</tr>
<tr>
<td>ampicillin</td>
<td>Injection: 500 mg (as sodium salt) in vial (<em>Section 6.2.1</em>)</td>
</tr>
<tr>
<td>benzylpenicillin (penicillin G)</td>
<td>Powder for injection: 600 mg (= 1 million IU); (sodium or potassium salt) in vial (<em>Section 6.2.1</em>)</td>
</tr>
<tr>
<td>cefotaxime</td>
<td>Powder for reconstitution: 500 mg (<em>Section 6.2.1</em>)</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>Powder for reconstitution: 250 mg (as sodium salt) in vial (<em>Section 6.2.1</em>)</td>
</tr>
<tr>
<td></td>
<td>* not in infants &lt;41 weeks corrected gestational age.</td>
</tr>
<tr>
<td>cloxacillin</td>
<td>Injection: 500 mg (as sodium salt) in vial (<em>Section 6.2.1</em>)</td>
</tr>
<tr>
<td>procaine benzylpenicillin</td>
<td>Suspension for intramuscular injection 1 g (<em>Section 6.2.1</em>)</td>
</tr>
</tbody>
</table>
## CORE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>erythromycin*</td>
<td><strong>Powder for oral liquid:</strong> 125 mg (as stearate or ethyl succinate) in 5 ml <em>(Section 6.2.2)</em></td>
</tr>
</tbody>
</table>
| gentamicin | **Injection:** 10 mg (as sulfate)/ml in 2-ml vial *(Section 6.2.2)*  
**Solution (eye drops):** 0.3% (as sulfate) *(Section 21.1)* |
| fluconazole | **Injection:** 2 mg/ml in vial  
**Oral liquid:** 50 mg/5 ml *(Section 6.3)* |
| nystatin | **Oral liquid:** 50 mg/5 ml or 100 000 IU/ml *(Section 6.3)* |
| zidovudine | **Oral liquid:** 50 mg/5 ml  
**Solution for injection:** 10 mg/ml *(Section 6.4.2.1)* |
| nevirapine | **Oral liquid:** 50 mg/5 ml. *(Section 6.4.2.2)* |
| phytomenadione | **Injection:** 1 mg/ml in 5 ml ampoule *(Section 10.2)* |
| methylrosanilinium chloride (gentian violet) | **Aqueous solution:** 0.5% *(Section 13.2)* |
| 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. *(Sections 17.5.1 and 26.1)* |
| antitetanus immunoglobulin | 500 IU vial *(Section 19.2)* |
| 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) *(Section 25.2)* |
| glucose | **Injectable solution:** 10% *(Section 26.2)* |
| potassium chloride | **Solution for injection:** 7.5% (equivalent to K 1 mmol/ml and Cl 1 mmol/ml) *(Section 26.2)* |
| sodium chloride | **Injectable solution:** 0.9% isotonic (equivalent to Na+ |
### CORE

<table>
<thead>
<tr>
<th>Compound</th>
<th>Level</th>
<th>Reference</th>
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<tbody>
<tr>
<td>water for injection</td>
<td>Solution for injection: 2-ml; 5-ml; 10-ml ampoules.</td>
<td>Section 26.3</td>
</tr>
<tr>
<td>cholecalciferol</td>
<td>Oral liquid: 400 IU/ml</td>
<td>Section 27</td>
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</table>

### COMPLEMENTARY

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>atropine sulfate</td>
<td>Injection: 1 mg (as sulfate) in 1 ml ampoule</td>
<td>Sections 1 and 4</td>
</tr>
<tr>
<td>hydrocortisone</td>
<td>Powder for injection: 100 mg (as sodium succinate) in vial</td>
<td>Sections 3 and 8.3</td>
</tr>
<tr>
<td>imipenem + cilastatin</td>
<td>Powder for injection: 250 mg (as monohydrate) + 250 mg (as sodium salt) in vial</td>
<td>Section 6.2.1</td>
</tr>
<tr>
<td>metronidazole</td>
<td>Injection: 500 mg in 100-ml vial</td>
<td>Sections 6.2.2 and 6.5.1</td>
</tr>
<tr>
<td>vancomycin</td>
<td>Powder for injection: 250 mg (as hydrochloride) in vial</td>
<td>Section 6.2.2</td>
</tr>
<tr>
<td>amikacin</td>
<td>Solution for injection: 50 mg/ml</td>
<td>Section 6.2.4</td>
</tr>
<tr>
<td>aciclovir</td>
<td>Solution for injection: 250 mg/10 ml</td>
<td>Section 6.4.1</td>
</tr>
<tr>
<td>amphotericin B</td>
<td>Injection: 50 mg in vial</td>
<td>Section 6.5.2</td>
</tr>
<tr>
<td>digoxin</td>
<td>Injection: 100 micrograms/ml</td>
<td>Oral liquid: 50 micrograms/ml</td>
</tr>
<tr>
<td>dopamine</td>
<td>Injection: 40 mg/ml as hydrochloride in 5-ml vial</td>
<td>Section 12.4</td>
</tr>
<tr>
<td>ranitidine</td>
<td>Injection: 25 mg/ml in 2-ml ampoule</td>
<td>Section 17.1</td>
</tr>
<tr>
<td>insulin</td>
<td>Injection: 100 IU/ml in 10-ml vial</td>
<td>Section 18.5</td>
</tr>
</tbody>
</table>

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