WHO Technical Report Series
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THE SELECTION AND USE OF ESSENTIAL MEDICINES

Report of the WHO Expert Committee,
October 2007
(including the Model List of
Essential Medicines for Children)

World Health Organization

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WHO Expert Committee on the Selection and Use of Essential Medicines

Geneva, 24–25 October 2007

Members

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

Dr Helena Coelho, Department of Pharmacy, Federal University of Ceará, Fortaleza, Brazil

Professor Noël Cranswick, Australian Pediatric Pharmacology Research Unit, Royal Children's Hospital, Parkville, Victoria, Australia

Dr Anwar-ul Hassan Gilani, National Professor of Pharmacology, Department of Biological and Biomedical Sciences, Faculty of Health Sciences, The Aga Khan University, Karachi, Pakistan

Mr Andy Gray, Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Congella, South Africa. (*Vice-Chair*).

Dr Usha Gupta, Executive Vice-President, Delhi Society for Promotion of Rational Use of Drugs, New Delhi, India

Dr Abdelkader Helali, Director, Centre National de Pharmacovigilance et Matériovigilance, Ministry of Health and Population, C.H.U. de Bab El Oued, Algiers, Algeria

Dr Kalle Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland

Dr Alar Irs, Deputy Director-General, State Agency of Medicines and University of Tartu, Tartu, Estonia

Dr Peter Kazembe, Baylor College of Medicine, Children's Clinical Centre of Excellence, Lilongwe, Malawi

Mr Dinesh Mehta, Therapeutic Review Group, Vigilance and Risk Management of Medicines, Medicines and Healthcare Products Regulatory Agency, London, England

Dr Marcus Reidenberg, Chief, Division of Clinical Pharmacology, Weill Medical College of Cornell University, New York, NY, USA. (*Chair*)

Dr Sri Suryawati, Director, Centre for Clinical Pharmacology and Medicine Policy Studies, Gadjah Mada University, Yogyakarta, Indonesia

Dr Susan Walters, Lyons, Australia. (*Rapporteur*)

Representatives of other Organizations

United Nations Children's Fund (UNICEF)

Mrs Hanne Bak Pedersen, Senior Adviser Pharmaceutical Policy, UNICEF Supply Division, Copenhagen, Denmark

Temporary Advisers

Dr Pisonthi Chongtrakul, Thai Board of Pediatrics, Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Dr Li Zhiping, Director, Department of Pharmacy, Children's Hospital of Fudan University, Shanghai, People's Republic of China

Dr Hidefumi Nakamura, Director of Clinical Research, National Children's Medical Centre, National Centre for Child Health and Development, Tokyo, Japan

Dr Jane Robertson, Senior Lecturer, Department of Clinical Pharmacology, University of Newcastle, Waratah, Australia

Secretariat

Dr Suzanne Hill, Scientist, Policy, Access and Rational Use/Medicines Policy and Standards WHO, Geneva, Switzerland (*Secretary*)

Dr Hans Hogerzeil, Director, Medicines Policy and Standards, WHO, Geneva, Switzerland

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

Dr Elizabeta Zisovska, Policy, Access and Rational Use/Medicines Policy and Standards, WHO, Geneva, Switzerland

Additional participants (for the determination of research priorities)

Ms Elin Haf Davies, European Medicines Agency, London, England

Dr Gregory Kearns, University of Missouri, Kansas City, MO, USA

Dr Donald Mattison, National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD, USA

Dr Dianne Terlouw, Liverpool School of Tropical Medicine, Liverpool, England

Declaration of interests

Members of the WHO Expert Committee on the Selection and Use of Essential Medicines reported the following:

Professor Noël Cranswick reported being an investigator for GlaxoSmithKline, Quintiles, Uriach, BioMarin and Biota in a number of pharmaceutical trials but that these trials did not concern any of the products (or related products) being considered at the present meeting. He also reported holding shares in Biota through a family trust.

Mr Andy Gray reported having accepted travel support and honoraria from AstraZeneca and Aspen Pharmacare for continuing professional development lectures, and being a study pharmacist for the International Clinical Trials Unit/Center for the AIDS Programme of Research in KwaZulu-Natal, South Africa, as well as being a co-investigator in a USAID-funded trial of a Gilead product. 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 GlaxoSmithKline and Leiras Ltd, Finland, and providing consultation advice to Lundbeck A/S Denmark through the Clinical Research Institute Helsinki University Central Hospital Ltd./Finnish Investigators Network for Paediatric Medicines.

Mr Dinesh Mehta reported being an employee of the British National Formulary, whose organization carries out editorial work on the *WHO Model Formulary*.

Dr Marcus Reidenberg reported having been a consultant for Roche on drug research and development and that he was currently serving as a member of a data safety and monitoring board for that company. He reported receiving royalties through the National Institutes of Health with respect to the use of gossypol for cancer, and also being a consultant to several start-up companies, none of which have products on the market.

Dr Susan Walters reported having been a consultant for an over-the-counter (OTC) medicine manufacturer and for solicitors acting for a generics company, and having received travel support from Novartis to present a training course to the Brazilian regulatory authority.

Mrs Jehan Mohammed Ali Al-Fannah, Dr Helena Coelho, Dr Anwar-ul Hassan Gilani, Dr Usha Gupta, Dr Abdelkader Helali, Dr Alar Irs, Dr Peter Kazembe and Dr Sri Suryawati reported no conflict of interest.

The Temporary Advisers reported the following interests:

Dr Pisonthi Chongtrakul reported that a family member was currently employed by GlaxoSmithKline. He also reported being an Expert Adviser for the Thai Food and Drug Administration on essential medicines, and in this capacity he had made numerous public statements on essential medicines.

Dr Hidefumi Nakamura reported having shares in a scientific company and, in his role as Director of Research for the National Centre for Child Health and Development, Japan, having been a medical adviser to Janssen Pharmaceutical K.K., the Japan Poliomyelitis Research Institute, Kyowa Hakko Kogyo Co. Ltd., Mitsubishi Tanabe Pharma, Kirin Pharma and Eli Lilly in selected pharmaceutical trials. He reported receiving no income from these activities, and that his institute supported industry-sponsored and investigator-initiated trials in Japan.

Dr Li Zhiping reported no conflict of interest.

1. Introduction

The WHO Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 24 to 25 October 2007. The meeting was opened on behalf of the Director-General by Dr Howard Zucker, Assistant Director-General for Health Technology and Pharmaceuticals. He welcomed participants to the meeting, noting that it was an extra meeting of the Expert Committee that coincided with the 30th anniversary of the first Expert Committee and Model List of Essential Medicines. On this occasion the meeting had been convened to review the findings of the Subcommittee meeting held in July. The Subcommittee meeting had drafted a provisional list of essential medicines for children and in order for this to be approved by the Director-General, the parent Committee was requested to consider the findings as described in the report.

Dr Zucker briefly explained some aspects of the procedures for Expert Committees. He reminded members that the Expert Committee 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 any other authority.

Dr Zucker reviewed certain aspects of the Subcommittee report and findings. He noted that, according to the approved terms of reference, the Subcommittee was required to prepare a list of medicines for children, based on clinical needs and the burden of disease, to allow the revision of the WHO Model List of Essential Medicines, and especially to include missing essential medicines for children. The provisional list of essential medicines presented to this meeting was the first step in the process, although it was clear from the report of the July meeting that additional work would be required to complete this task. He also noted the extensive list of research gaps identified in Appendix 5 of the meeting report. Dr Zucker highlighted the importance of the discussion at an informal meeting held on 23 October 2007, to prioritize these requirements as a guide to manufacturers wishing to develop new essential medicines for children. He commended the report of the Subcommittee meeting to the Expert Committee and looked forward to the outcome of their deliberations.

Dr Hans Hogerzeil, Director of the Department of Medicines Policy and Standards, also addressed the Expert Committee. He stated that as this year is the 30th anniversary of the Essential Medicines List regional meetings were taking place over the same period to celebrate the programme, in Mozambique, Peru and Sri Lanka. All of these countries were early proponents of the essential medicines concept and its role in improving health outcomes. He commented that the work of the Subcommittee on

Essential Medicines for Children was part of a major programme to improve access to better medicines for children and looked forward to receiving the report on discussion at the meeting.

The WHO Secretariat requested and received agreement from the Expert 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 draft WHO Model List of Essential Medicines for Children (EMLc). Furthermore, for Expert Committee members it provided an opportunity to receive, at first-hand, additional information and opinion on matters under consideration.

For this meeting report, the Expert Committee decided to use a slightly different format. The report of the Subcommittee meeting and the provisional list of essential medicines for children as drafted in July are presented in Annex 2. The Expert Committee discussion of the proposal forms the main body of the present report.

The full texts of the comments received are not included in the report but remain available on the WHO web site, and are accessible through the Essential Medicines Library (http://www.who.int/emlib).

2. Open session

This session of the meeting was opened by Dr Howard Zucker, Assistant Director-General for Health Technology and Pharmaceuticals, on behalf of the Director-General. He welcomed participants to the meeting, noting that it coincided with the 30th anniversary of the first Expert Committee and Model List of Essential Medicines. He reminded participants that all comments made during the open session would be noted and taken into consideration by the Expert Committee when formulating final recommendations in subsequent private sessions.

Dr Zucker noted that this meeting of the Expert Committee on the Selection and Use of Essential Medicines had been convened to review the findings of the Subcommittee meeting held in July. The Subcommittee meeting had drafted a provisional list of essential medicines for children and in order for this to be approved by the Director-General, the parent Committee was requested to consider the findings as described in the report. The Model List of Essential Medicines is a key tool in guiding procurement and availability in many countries and he anticipated that, with adoption of the Essential Medicines List for Children, there will be new interest and activity in essential medicines programmes generally.

Dr Hans Hogerzeil, Director of the Department of Medicines Policy and Standards, also addressed the meeting. He stated that, to mark the 30th anniversary of the Essential Medicines List, regional meetings were taking place over the same period to celebrate the Essential Medicines Programme, in Peru, Mozambique and Sri Lanka. All of these countries were early proponents of the essential medicines concept and its role in improving health outcomes. He highlighted the successes of the programme, including almost universal adoption of the essential medicines concept by Member States and international pharmaceutical programmes, increasing access to essential medicines, adoption of national medicines policies, and provision of information to Member States, including for example sources and prices of medicines. He listed some of the achievements in relation to normative activities, traditional medicines, pharmacovigilance, rational use of medicines, and highlighted in particular the outstanding work of the Expert Committee on Specifications for Pharmaceutical Preparations. The WHO Prequalification Project is a major initiative that has made real progress in making high-quality medicines available internationally.

As part of the open session, participants were briefed about various activities relating to the work on essential medicines for children. A number of issues were raised and debated during the open session.

Dr Suzanne Hill provided background to the meeting, explained the WHO rules governing Expert Committee processes and identified the expected outcomes of the meeting. She noted that there are few precedents for WHO Expert Subcommittees, but it would be anticipated that the Expert Committee would review the provisional list of medicines for children and endorse the publication after having also considered the comments that have been received from individuals and applicants, which have been posted on the WHO web site.

Presentation of the Subcommittee Report

Mr Andy Gray, Chair of the Subcommittee, presented the key outcomes of the July meeting. He drew the Expert Committee's attention to a number of key points in the Subcommittee report including:

- The general considerations in relation to essential medicines for children (see Section 3, Annex 2), particularly the following points that the Subcommittee noted at the end of its meeting:
  - — The difficulty of making decisions on many medicines because of lack of data
  - — The lack of data on disease burden for sub-groups of children

— The need to include oral liquid forms to ensure very young children can be treated
— Difficulties in determining the licensing status for specific age groups of many medicines
— Lack of information as to suitable dosage forms

There are additional symbols included in the provisional list to indicate known age restrictions as well as the need for additional information.

Mr Gray also noted that the current approach to use of square boxes had generally been retained, but for some products that have a square box in the 15th WHO Model List it was not appropriate to maintain the symbol with respect to use in children. This might lead to some apparent inconsistencies between the 15th List and the provisional list for children and he asked the Expert Committee to consider how this might be resolved.

Mr Gray advised the Expert Committee that a number of new applications for medicines for children had been considered by the Subcommittee, as well as the application specifically referred to it by the March meeting of the Expert Committee. The considerations of these applications are provided in the relevant sections of the report. Mr Gray particularly noted that, on review of additional evidence, the Subcommittee had recommended the inclusion of rectal artesunate; and that on the basis of additional evidence, the addition of subcutaneous immunoglobulin for very specific indications was recommended. The other applications considered by the Subcommittee were not recommended for inclusion at this time, and the full considerations of them are described in the report.

Mr Gray pointed out that some of the applications had been for very specific amendments to existing dosage forms, such as changing the specification of a ‘tablet’ to a ‘scored tablet’. Clearly the change had potential implications for better use of the medicines in children, especially for those products that were changed from an unscored tablet to a scored one, for example. However, the Subcommittee had some difficulty in determining whether there was a need to specify this level of detail, as at the March meeting more general terms were accepted. The Expert Committee was asked to consider this general principle further.

The Subcommittee had identified what appeared to be an anomaly in the 15th List in relation to medicines for filariasis. Suramin sodium is listed as a complementary medicine but is not recommended for this indication. The Subcommittee had therefore recommended that this medicine should not be endorsed as essential for children and had also recommended that its continued listing for adults should be reviewed.

Finally, Mr Gray drew the Expert Committee's attention to the comments submitted on the provisional list and reports by many individuals as well as some of the applicants. Some were extensive and detailed and he thanked the contributors for their thoughtful reviews. He commended the provisional List of Essential Medicines for Children to the Expert Committee for its consideration.

Report on the Informal Consultation on Research Priorities for Children's Medicines

Given the extensive list of research gaps identified by the Subcommittee, an informal meeting to discuss strategies for setting priorities for research had been held on 23 October 2007. A preliminary report of that meeting was presented. The Secretariat had conducted a survey of paediatricians, pharmacologists and Expert Panel members to try to set some priorities in the extensive list of research topics. The report of the meeting is provided as Annex 1.

Other matters

Additional work on medicines for children carried out by WHO in the last several months was also presented. A preliminary review of essential medicines specifically for neonates has begun as it had been identified as one of the major gaps at the meeting in July. This is considered further in Section 3 of this report.

Dr Sabine Kopp and Ms Marie Rabouhans of the Department of Medicines Policy and Standards reported on normative activities in relation to quality specifications and manufacturing. Dr Kopp described the role of the Expert Committee on Specifications for Pharmaceutical Preparations, and the mechanism by which new guidelines and lists are generated. She emphasized the broad nature of the Expert Committee's activities, and the large numbers of national, regional and international partners who provide expert input, ensuring outcomes that are acceptable at an international level. She explained how the Expert Committee on the Selection and Use of Essential Medicines could obtain advice and assistance from the Expert Committee on Specifications in relation to the quality of medicines, including those intended for use in children. Ms Rabouhans outlined the content of the International Pharmacopoeia (PhInt) and its role in defining the quality of medicines. She noted that the PhInt now focuses on medicines that are on the WHO Model List of Essential Medicines and those that are used in the treatment of priority infectious diseases, HIV/AIDS, TB and malaria.

Participant statements

Participant statements were received from:

— Ms Elin Haf Davies, European Medicines Agency (EMEA)
— Dr Jean-René Kiechel, Project Manager, DNDi
— Dr Seyberth, German Society of Paediatrics and Adolescent Medicine (DGKJ)
— Dr Eva Ombaka and Mr Albert Petersen, Ecumenical Pharmaceutical Network (EPN)
— Dr Myriam Henkens, Médecins Sans Frontières (MSF)

In their absence, the Secretariat read the statements of Dr Ombaka, Mr Petersen and Dr Henkens. The EPN thanked WHO for the support and guidance it had received — in the form of information materials, tools, publications and technical advice — and requested continued support of this nature. Médecins Sans Frontières made a number of comments that will be considered by the Expert Committee.

On behalf of DNDi and its partners, Dr Kiechel outlined recent progress in the development of a fixed-dose combination antimalarial drug containing artesunate and amodiaquine, which is intended to provide the simplest possible dosing regimen while ensuring delivery of safe and effective drug levels across all age groups. In partnership with Sanofi-Aventis, the product will be made available at cost to the public sector. Dr Kiechel drew participants' attention to the findings of a comparative study (involving artemether + lumefantrine) that demonstrated that the new combination exhibited a high level of efficacy, and also non-inferiority to an alternative combination.

Speaking on behalf of the DGKJ, Dr Seyberth proposed that the aims of the Model List of Essential Medicines for Children would be better served if it were to have a more international flavour, a broader target population, additional consideration of adolescent medicines and orphan diseases, and a structure more appropriate to paediatric needs. He discussed some specific examples. In concluding, he suggested that it would be better to develop a more general road map for improved medicines for all children in the world, rather than follow the current, albeit more practical, approach of simply searching for age appropriate formulations.

Finally, Ms Davies of the EMEA provided an update on the progress of European Union legislation relating to improving access to medicines for children, and welcomed the opportunity to collaborate with WHO.

3. Review of the report of the Subcommittee (including the provisional Model List of Essential Medicines for Children)

3.1 General issues

The Expert Committee considered the report of a recent meeting (July 2007) of the Expert Subcommittee (attached as Annex 2) and noted in particular the following matters.

- The general considerations in relation to essential medicines for children (see Annex 2, Section 3), particularly the points that the Subcommittee noted at the end of its meeting.

The Expert Committee recommended that the Subcommittee should also:

- review the format of the EMLc to make it more easily understood by users;
- consider how to ensure that paediatric needs remain prominent when, as anticipated, the EMLc is merged with the Model List.

The Expert Committee considered the question of the use of "square boxes" in relation to the EMLc. It was noted that the current system of using square boxes had been retained. However, in developing the list of essential medicines for children, the Subcommittee had found that for some medicines it was not appropriate to retain the square box annotation with respect to their use in children. Haloperidol was cited as a case in point: haloperidol, which is listed with a square box in the 15th WHO Model List, is included in the provisional model list of essential medicines for children but without a square box symbol.

Such apparent inconsistencies between the two lists arise because a square box annotation with respect to use in adults may not always be directly extrapolated to use in children. For instance, there are some medicines that can be interchanged in adults but that should not be interchanged in children; for others, the lack of substantiating data relating to interchangeability of therapeutically equivalent medicines in children makes this practice unacceptable.

Some discordance between the lists in terms of the use of the square box is therefore to be expected. The Expert Committee noted that some of these discrepancies might well be resolved once the planned reviews of various sections of the Model List have been completed. For the time being, however, while the two lists were separate, any such apparent inconsistency was not considered to be a significant problem as the meaning and criteria

for a square box annotation were the same in both. It was recognized that, when the two lists were amalgamated, there would be a need to identify those medicines for which the square box would not be applicable to all age groups. The Expert Committee therefore decided that any discrepant square box medicines should be reviewed in 2009, after the provisional EMLc had been updated.

The Subcommittee had reported that a number of recent applications for changes to the provisional EMLc had been for very specific amendments to the dosage forms of listed medicines — for example, requests for a change from "tablet" to "scored tablet" on the grounds that scored tablets allow more accurate dosing in cases when a half dose is required. Recognizing the potential implications of specifying scored tablets, the Subcommittee had requested that the Expert Committee consider this aspect and also the more general issue of the level of detail required — with respect to dosage forms — for all medicines on the Model List.

The Expert Committee considered the question of whether or not there was a need to be more specific about dosage forms, and in particular, whether or not to specify "scored" tablets, when previously more general terms had been acceptable. It was noted that ideally scored tablets should be produced for all medicines used in children, as they allow some degree of accurate dosing and thus better use of medicines in children overall. The Expert Committee decided that rather than specifying this for all products, a more general statement should be included in the preamble to the Model List pointing out that scoring is desirable for any tablet for which half a dose is specified in prescribing information for one or more populations. Information as to the consistency of half doses should be generated in each case.

In the open session, the Expert Committee's attention had been drawn to what appeared to be an anomaly in the current Model List, with respect to medicines for filariasis. Suramin sodium is included in the 15th WHO Model List as a complementary medicine for the treatment of filariasis, but is not recommended for this indication. At its July 2007 meeting, the Subcommittee had recommended that suramin sodium should not be endorsed as essential for children and furthermore, that its continued listing for adults be reviewed. On the basis of the Subcommittee's recommendations regarding its use in filariasis, the Expert Committee decided to mark suramin sodium for "fast-track" deletion at the next regular Expert Committee meeting.

The *WHO Model Formulary*

The Secretariat provided the Expert Committee with a brief update on progress on the 2008 edition of the *WHO Model Formulary*, including the

proposed development of a separate formulary for children's medicines. The intention is to form an editorial group, drawn from members of the Expert Panel and other interested individuals, to oversee the preparation of both products. The editorial group would "meet" electronically. Its primary function would be to provide guidance on the content of the new formulary and a degree of peer review as it is being prepared. It is hoped that in this way the entire existing document could be revised on a rolling basis, and a hard copy edition published every two years, in tandem with the Model List updates.

The Expert Committee endorsed this proposal and recommended that the Secretariat seek names, contact details and areas of expertise for nominees for the group.

The Expert Committee considered the question of the use of fixed-dose combination products (FDCs) in children as discussed in the Subcommittee report (see Annex 2, 3.2, page 44). It was agreed that WHO's *Guidelines for Registration of Fixed-dose Combination Medicinal Products* (*1*) adequately covered the questions raised.

The Expert Committee noted that the following general monographs for dosage forms already exist in the *International Pharmacopoeia* (*2*):

- capsules
- tablets
- ophthalmic preparations
- parenteral preparations
- topical semi-solid preparations.

The Expert Committee formally requested the Expert Committee on Specifications for Pharmaceutical Preparations to develop urgently general monographs for dosage forms that are relevant to paediatric medicines, such as:

- oral liquids, including powders for reconstitution into oral liquids
- rectal preparations including rectal capsules
- intranasal preparations
- enemas
- topical liquid dosage forms
- powders and multiparticulate preparations not covered elsewhere (e.g. "dose sticks")
- nebulizers.

It was considered that, in due course, general monographs for the following dosage forms would also be useful:

- metered dose inhalers

- dry powder inhalers
- transdermal patches.

The Expert Committee further requested that the general monograph for tablets should stipulate that, if tablets are scored, a test for uniformity of the delivered dose in halved tablets must be performed.

3.2 Review of matters referred to the Subcommittee

At its March 2007 meeting, the Expert Committee considered an application from WHO's Global Malaria Programme (GMP), to add rectal artesunate, as well as artesunate injection, to the Model List. The report of that meeting states (*3*):

> *The Committee noted the potential value of rectal dosage formulations and overall the evidence provided in the application supports the public health need, effectiveness and safety of artesunate formulations for emergency use in adults and children for treating severe malaria. However, the Committee noted that the regulatory status of the products, particularly the rectal capsule, was unclear. The Committee therefore recommended that artesunate ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution be added to the core list of the 15th WHO Model List with the note: "for use in the management of severe malaria". The Committee decided, given uncertainty about current rectal products, to refer review of the rectal form to the paediatric Subcommittee meeting and recommended further research on rectal dosage forms.*

A full account of the Subcommittee's consideration of this application can be found in Annex 2, page 75. In addition to the evidence submitted with the original application, the Subcommittee considered the findings of a new systematic review of the effectiveness of rectal administration of artemisinin derivatives, which had been published in June 2007 (*4*). The authors of the latest review had identified 20 published and three unpublished studies on the use of rectal forms of artesunate (50 mg and 200 mg suppositories) in both severe and uncomplicated malaria, plus a further two unpublished studies involving the Scanpharm product. Of these 25 studies, 18 published and five unpublished studies were included in the review. Ten of the identified studies included children (n = 481 total). Doses used were stratified into < 5 mg/ kg and > 5 mg/kg. On the basis of the additional clinical evidence, the Subcommittee concluded that there is sufficient clinical evidence to support the effectiveness of rectal artesunate suppositories as a pre-referral treatment in cases of severe malaria at doses of 10 mg/kg, although it recognized that the interpretation of these data is hampered by the limited quality of the trials.

At the present meeting, the Expert Committee noted the substantial body of evidence relating to the use of rectal forms of artesunate (based on two different products) and, in particular, the clinical evidence of its safety and effectiveness. The Expert Committee thus accepted the Subcommittee's recommendation that artesunate, rectal dosage form, 50 mg and 200 mg, be added to the Model List/EMLc. The listing should include a note that the preparation is only to be used as a single dose for pre-referral treatment and that children must be taken to an appropriate health facility for follow-up care.

3.3 Review of recommended additions to the list for children

3.3.1 *Subcutaneous immunoglobulin*

The Expert Committee considered the recommendation to add subcutaneous immunoglobulin to the list based on a new application in July, noting the considerations of these applications provided in the relevant sections of the report (Annex 2, page 87). On the basis of additional evidence, the addition of subcutaneous immunoglobulin for very specific indications had been recommended by the Subcommittee.

The Expert Committee noted that at present at least one nation recommends imposing a lower age limit of two years on the subcutaneous administration of immunoglobulin, but not on the use of the drug itself. However, no such restriction was found in the prescribing information from other jurisdictions. It was also noted that the clinical study, submitted in support of the application, had involved subjects as young as six weeks. After discussion, the Expert Committee agreed with the earlier recommendation of the Subcommittee that there is no reason to restrict paediatric use of immunoglobulin by imposing a minimum age limit for subcutaneous administration.

The Expert Committee thus endorsed the Subcommittee's recommendation regarding the subcutaneous use of immunoglobulin without age restriction. It also recommended that the two lists, the EMLc and the 15th Model List, should be consistent in terms of their listing of the specific indications for the use of intravenous and intramuscular immunoglobulin, in accordance with the recommendations of the Subcommittee (Annex 2).

3.4 Review of responses from applicants to recommendations made by the Subcommittee

3.4.1 *Artemether injection*

The submission for the inclusion of artemether (intramuscular injection, 20 mg/ml) was considered at the July 2007 meeting of the Subcommittee. At that time, the application was rejected on the following grounds:

- uncertainties about the pharmacokinetics, pharmacodynamics, clinical efficacy and safety of Miglyol®-based artemether, 20 mg/ml, in children, especially given the variable absorption of injectable artemether generally;
- the majority of studies submitted in support of the proposal involved small numbers of adults and provided only scant methodological details;
- some published studies on the use of intramuscular artemether were not included in the application;
- cost; the cost of the new product is double that of parenteral quinine.

In response, the applicant presented the following points:

- athough some relevant studies were not retrieved by the original search strategy, their omission does not alter the conclusion of the original application;
- a more complete report of a study previously submitted, on the pharmacokinetics of artemether in Miglyol® compared with artemether in arachis oil, is now available;
- the product has been submitted to the WHO Prequalification Programme rather than to the EMEA.

The new report presented to support the application is an unpublished manuscript outlining the results of the Dafra study, which had been carried out in Côte d'Ivoire in 23 patients with uncomplicated malaria, aged 16 years and above. The study compared Dafra's 80 mg/ml injection and an equal strength injection purchased in Abidjan. The primary endpoint was plasma levels of artemether and dihydroartemesinin (DHA).

The study was an open one and, according to the report provided, does not appear to have been randomized. Sampling frequency and methods were not described in detail. Neither were the individual patient data for plasma concentrations provided, which made independent analysis of the results difficult. However, it appeared that several subjects had been excluded from the graphical presentation of results and, judging by the graphs provided, there was considerable interindividual variation in plasma DHA concentrations.

The claimed lack of difference between the two products seems to have been based on visual comparison of tabulated and graphical data. The statement that concentrations of DHA were "never more than 10% of the level of artemether" appears to have been based on the graphs of mean concentrations. However, the assayed concentrations of DHA were in the main below the validated assay range. In the 21 samples where the concentration of DHA was measurable, it was always more than 10% of

the concentration of artemether. For these reasons, the Expert Committee concluded that the study did not demonstrate equivalence of the two vehicles. As the major uncertainty about this product concerns the kinetic profile related to the vehicle, there is no basis for altering the recommendation made by the Subcommittee in July.

The difficulty in conducting bioequivalence studies on high variance drugs was noted. This is an important question that is being studied globally. The Expert Committee recommended that WHO be involved in such endeavours, in order to bring a global perspective to the matter.

3.4.2 *Artesunate + amodiaquine*

The meeting of the Subcommittee in July considered an application from Sanofi and DNDi for the inclusion of a new fixed-dose combination (FDC) product containing artesunate and amodiaquine, in three strengths: 25 mg + 67.5 mg, 50 mg + 135 mg, 100 mg + 270 mg. The dose of amodiaquine in the proposed FDC product is lower than that currently recommended in WHO treatment guidelines for use of the two components in loose combination (*5*).

The Expert Committee reviewed the Subcommittee's report regarding the application (see Annex 2, page 77), noting in particular its comments on the review of available clinical data. Much of the data had come from a single study, the unpublished Burkina Faso study, and this was the main study that was cited in support of the application.

The Expert Committee then reviewed the responses that it had subsequently received from the applicants, considering each point in turn as noted below:

- ***Dose ratio***
  Responses from both applicants (DNDi and Sanofi) cite a published article by Taylor et al. (*6*), which had been included in the original application, as the justification for the choice of dose ratio in the proposed FDC product. Adopting a new methodology, this study used a weight-for-age database from a sub-Saharan Africa population to model the optimal strength for the artesunate + amodiaquine combination tablet. The key assumptions and variables employed in this model include:

  — the therapeutic range for the dose of amodiaquine is 7.5–15 mg/kg/day (on the basis of an analysis of selected studies);
  — the therapeutic range for the dose of artesunate is 2–10 mg/kg/day;
  — standardizations for age, weight and malaria risk, with weighting factors that are specified although not completely justified.

According to this model, the "optimal" strengths of amodiaquine in the combination are between 67 and 69 mg (base for paediatric tablets) and between 260 mg and 290 mg (base for adult tablets), with corresponding values of artesunate of between 26 mg and 29 mg, and 102 mg and 116 mg, respectively. The "optimal ratio" of the two components is calculated as 2.7. Table 2 of Taylor et al.'s article, reproduced by Sanofi, is the key result on that basis: it is suggested that for the proposed FDC, the proportion of patients who receive a dose within the recommended therapeutic range is greater than that for the loose combination.

The Committee conceded that the model may be a plausible basis for the choice of component strength in the proposed FDC. However, the key uncertainty in the model that would need to be checked is the estimated therapeutic dose range for amodiaquine, which, as noted above, varies two-fold. The selection of the dose range should be based on a comprehensive review of all available studies, but it was difficult to determine whether or not this had been done from the information provided in the published article. A sensitivity analysis, in which the effective dose was varied, would be an alternative approach.

- ***Selection of studies presented in the application***
  The Subcommittee had noted (see Annex 2) that several potentially relevant studies had been excluded from the original application. The applicant responded that they had intentionally confined their attention to those studies that concerned products manufactured by Sanofi so that quality could be guaranteed.

- ***The quality of the Burkina Faso study***
  The Subcommittee was unable to comment in detail on the quality of the study from which much of the supporting evidence for the application comes, as the study report is as yet an unpublished document, and still marked as confidential. The Expert Committee recommended that any concerns regarding study quality be provided by the Secretariat directly to the applicant.

- ***The quality of the product and concerns about confidentiality***
  In its report, the Subcommittee had raised the matter of product quality and confidentiality (see Annex 2). These comments were based on a public discussion on e-drug (electronic discussion group). The Expert Committee noted that in its response DNDi had advised that the product had not yet met all of the WHO Prequalification Programme requirements.

- ***Additional study***
  The response referred to a new study, outline details of which had been provided (as a Powerpoint presentation) to the Subcommittee immediately

prior to its July 2007 meeting. A preliminary written report of the new study was available to the Expert Committee at the present meeting. It has been published on the meeting web site after confirmation by Sanofi that it was acceptable to do so.

The new study is a randomized observer-blind multi-centre study involving 941 subjects with uncomplicated malaria, in which the effectiveness of the proposed artesunate + amodiaquine FDC (given once or twice per day, but dose and frequency were not fully explained in the summary) was compared with that of artemether + lumefantrine FDC. The primary endpoint was PCR-corrected parasitaemia at 28 days. It was not clear from the information provided whether the study was designed as a superiority or non-inferiority study (see Table 1).

Table 1

Multi-centre study comparing the effectiveness of artesunate + amodiaquine with artemether + lumefantrine in uncomplicated malaria: results for the primary endpoint

	Primary endpoint (%)	
Regimen	**ITT population**	**Per protocol**
Artesunate + amodiaquine, FDC once daily dose	95.2 (n=310)	98.9 (n=238)
Artesunate + amodiaquine, FDC twice daily dose	94.9 (n=315)	100 (n=285)
Artemether + lumefantrine	95.5 (n=311)	98.6 (n=289)

A full evaluation of this study would require a more complete report.

The Expert Committee was advised that a systematic review of studies on artesunate and amodiaquine had been submitted for publication. However, in its present form, the manuscript does not provide data on the efficacy of the combination, stratified by dose. A meta-analysis of individual patient data is planned; it is anticipated that this will include an analysis of the dose of amodiaquine, which may be of interest to the Expert Committee. The DNDi presentation at the open session identified a third study in progress.

The Expert Committee considered the overall weight of evidence available at this time. Noting the uncertainty about whether the dose of amodiaquine in the proposed FDC is clinically equivalent to that which is currently used and the lack of a quality-assured product at this time, the Committee decided there was insufficient evidence to modify the Subcommittee's recommendation, made in July, to reject the application.

Given the data that are under development, the Committee considered the application to be premature at this time, but indicated that it would welcome a resubmitted application as soon as the anticipated data became available. Discussion of this product emphasized the need for a procedure for making decisions via electronic consultation in circumstances when additional relevant data were likely to become available before the next meeting.

3.4.3 *Artemether + lumefantrine*

The original submission for inclusion of artemether + lumefantrine, powder for suspension, 120 ml (containing 360 mg artemether + 2160 mg lumefantrine), from Dafra Pharma was first considered by the Expert Committee in March 2007. The proposed dosing regimen (see page 8 of the original application) is shown in Table 2.

Table 2

Proposed dosing regimen for artemether + lumefantrine, powder for suspension

Body weight (kg)	Dose (ml)		
	Day 1	Day 2	Day 3
5	7	7	7
7.5	10	10	10
10	14	14	14
15	20	20	20

The original application was supported by three studies, all of which were considered to be of relatively poor quality (i.e. uncertain or open single-arm design, non-randomized). The applicant also submitted advice that a bioequivalence study was being carried out and that two additional clinical trials, comparing the suspension with the standard tablet formulation, were planned.

A comparison of the proposed suspension and the conventional tablet formulation, in terms of the dose of artemether provided per day and per course, is shown in Table 3. *For the smallest children, weighing 5–10 kg, the dose of artemether is significantly different*. The proposed suspension-based regimen is based on a once daily dose for 3 days, rather than the standard 6-dose regimen that has a 'loading' dose in the first 24 hours (*5*).

Dose-ranging studies — to establish that the proposed dosage regimen for the suspension is effective across all weight bands of children — have yet to be performed or reported. The proposed dosing schedules mean that the suspension formulation provides a lower mg/kg dose per day and mg/kg

dose per course for children weighing 5–10 kg, and higher treatment course dose for children weighing 14–15 kg, than the currently recommended tablet-based regimen (*5*). In addition, the difficulty of administering accurate doses of the suspension in the absence of syringes was noted.

Table 3
Treatment doses of artemether for children, by formulation

Weight of child (kg)	Dose of artemether			
	Dose per day (mg)	Dose per course (mg)	Dose per day (mg/kg)	Dose per course (mg/kg)
Tablet[a] *(20 mg artemether + 120 mg lumefantrine)*				
5	60 (3 tablets)	120 (6 tablets)	12.0	24.0
10	60 (3 tablets)	120 (6 tablets)	6.0	12.0
14	60 (3 tablets)	120 (6 tablets)	4.3	8.6
Suspension (3 mg artemether + 18 mg lumefantrine per ml)				
5	21 (7 ml)	63 (21 ml)	4.2	12.6
7.5	30 (10 ml)	90 (30 ml)	4.0	12.0
10	42 (14 ml)	126 (42 ml)	4.2	12.6
15	60 (20 ml)	180 (60 ml)	4.0	12.9

[a] WHO *Guidelines for the treatment of malaria*, 2006 (*5*).

At its meeting in March 2007, the Expert Committee rejected the application to add the artemether + lumefantrine suspension on the grounds of inadequate evidence of efficacy of the proposed dosing regimen.

The application was resubmitted to the July 2007 Subcommittee meeting, re-presenting the same three clinical trials considered in March, plus the unpublished results of a recent bioequivalence study (with Coartem tablets). The information provided in the application in relation to the bioequivalence study did not allow independent assessment of the validity of the results, which were claimed to show that the two products are bioequivalent. The Subcommittee thus rejected the resubmitted application on the grounds of insufficient clinical evidence. It was suggested that further applications for the product should not be considered without additional high-quality clinical trials of sufficient size, or other substantial evidence (see Annex 2, page 73).

At the present meeting, the applicant argued that the suspension product should be regarded as a generic substance, and that their product is equal to the originator product in terms of efficacy, safety and bioequivalence.

In addition, the applicant suggested that the suspension offers a distinct advantage over other formulations, permitting accurate individual dosing (using a graduated plastic cylinder cup), and that it has the same efficacy as a single daily dosing regimen. However, they did point out that they were not recommending a dosing regimen that would be comparable with that currently recommended for artemether + lumefantrine tablets, acknowledging that if the dose were adjusted to be equivalent, the volumes of syrup could become a problem in some heavier children.

The applicant argued that since the proposed dose of artemether is equivalent to the recommended dose of artesunate (4 mg/kg/day), their suspension product is likely to be effective. However, no new clinical data were provided to support this claim. Some pharmacological evidence was provided, but this did not take into account the pharmacokinetic differences between the two substances, although both are metabolized to the active metabolite, dihydroartemisinin.

The Expert Committee noted that no new substantive clinical evidence had been provided in support of the application since its previous review in March. It considered that three key questions remain unanswered:

- Is the dose of artemether as proposed in the preparation effective?
- Is a single daily dosing regimen equivalent to the currently recommended dosing regimen (i.e. a loading dose followed by a lower maintenance dose)?
- Can therapeutic equivalence be accepted on the assumption that since both drugs are metabolized to the same active principle, equal doses of the separate parent compounds give identical clinical effect? This question is raised because of a lack of information in the application about the fraction of the dose of the parent compounds that is converted to the active principle, and the significance, if any, of the potential differential plasma concentration profile of dihydroartemisinin.

In the absence of data that addresses these questions, the Expert Committee remained of the view that there is insufficient evidence of effectiveness, safety and suitability of the proposed suspension and therefore it should not be added to the EMLc. The Expert Committee endorsed the recommendation of the Subcommittee that future applications should not be considered without additional clinical trials of acceptable quality and sufficient size, or other substantial evidence.

3.4.4 *Artesunate + mefloquine*

The application, submitted by Mepha Pharma, for the inclusion of a FDC product containing 50 mg artesunate (as pellets) and 125 mg mefloquine

(as powder) for use in children weighing 10–20 kg was first considered at the July 2007 Subcommittee meeting. The original application included a review of the results of four pharmacokinetic studies, two randomized trials (which compared different dosing regimens), and five investigator-initiated post-marketing studies. The evidence provided specifically for the proposed product was based on a single study from Gabon of insufficient statistical power.

Table 4 summarizes the recommended dosing schedule for this drug combination (artesunate and mefloquine), according to the current WHO treatment guidelines (*5*).

Table 4

Dosing schedule for artesunate and mefloquine combinations, in mg

(the equivalent number of tablets, assuming the tablets contain 50 mg artesunate and 250 mg mefloquine is given in parentheses)

Age	Artesunate			Mefloquine		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5–11 months	25 (1/2)	25	25	–	125 (1/2)	–
≥ 1–6 years	50 (1)	50	50	–	250 (1)	–
≥ 7–13 years	100 (1)	100	100	–	500 (2)	250 (1)
> 13 years	200 (1)	200	200	–	1000 (4)	500 (2)

Source: *Guidelines for the treatment of malaria. Geneva, World Health Organization, 2006.*

According to the current WHO guidelines, treatment regimens based on single daily doses of 25 mg/kg of mefloquine are associated with increased adverse events and therefore the split dose is recommended. The guidelines also state that a lower dose of mefloquine (i.e. 15 mg/kg) is not as effective as a higher dose and therefore should not be used (*5*).

The proposed dosing regimen is one "stick pack" (containing artesunate, 50 mg + mefloquine, 125 mg) per day for three consecutive days. It was noted that use of a once-daily dose could potentially lead to more adverse reactions, and furthermore, as mefloquine has a very narrow therapeutic index, that the proposed FDC would overdose a 10-kg child and significantly under-dose a 20-kg child (see Annex 2, page 81). Product-related safety data obtained during the post-marketing period were not provided in detail with the application.

At its July meeting, the Subcommittee rejected this application on the grounds of considerable uncertainty with regard to the appropriateness of the dose of mefloquine in this FDC.

Arguments presented by the applicant in response, include the following:

- The proposed FDC product has proven pharmaceutical equivalence with existing co-blistered formulations.
- The dosages of artesunate and mefloquine for children weighing between 10 and 20 kg had been based on WHO guidelines (*5*) and the WHO Child Growth Standard Tables for Weight-for-Age, and the targeted dose set to a mean body weight of 15 kg. The proposed formulation would thus provide a smaller dose range than that currently recommended for mefloquine monotherapy for children, according to the *Summary of Products Characteristics of Lariam and Mephaquin*. To date, no adverse drug reaction reports had been received.
- The product should be considered as a line extension of the existing Artequin co-blistered oral dosage formulations, rather than a new dosage form and strength.

The applicant also submitted a published pharmacokinetic study as a late addendum to their response. The Expert Committee noted that the new study was difficult to interpret.

The Expert Committee noted that no substantive new evidence about the appropriateness of the dose of mefloquine in the proposed combination had been provided and therefore uncertainty about the safety and efficacy of the proposed combination has not been resolved. Arguments about co-blistered products were not considered to be relevant as they are not normally specified separately in the Model List. Moreover, no evidence as to the dose accuracy of half stick-pack doses that would be required in certain situations was supplied. The Expert Committee thus concluded that there is no basis to amend the Subcommittee's July recommendation to reject the application.

3.4.5 *Racecadotril*

The application to add racecadotril, submitted by Bioproject Pharma, was first considered by the Subcommittee at its meeting in July. Racecadotril (acetorphan) is an enkephalinase inhibitor with antisecretory and antidiarrhoeal actions, which is to be used in conjunction with oral rehydration solution for the treatment of watery diarrhoea. It was proposed for use in all patients, including young children (i.e. from one month upwards) except those with renal or hepatic impairment, and patients with fructose intolerance, glucose malabsorption syndrome or saccharase–isomaltase deficiency.

Evidence for the effectiveness of racecadotril stems largely from two randomized controlled trials, which had been conducted in the hospital setting. The original application also provided some data from post-

marketing pharmacovigilance activities that suggest that the most frequent adverse events associated with racecadotril are cutaneous and/or allergic reactions (i.e. rash, erythematous/papulous reaction, prurigo and urticaria). While these studies indicate a benefit of racecadotril therapy, as an adjunct to oral rehydration therapy (ORT) in reducing stool output in subjects with severe diarrhoea/dehydration, both were conducted in hospital settings and under rigorous trial conditions. It is difficult to generalize these findings and thus assess the value of racecadotril therapy outside of the hospital setting, and in less severely affected infants. Experience with the use of racecadotril remains limited: only 307 infants participated in the two trials cited in the application. Concerns were also raised about the possibility of unpublished negative trials. For these reasons, the Subcommittee decided that, as yet, there are insufficient clinical data to support the inclusion of racecadotril in the EMLc.

The Expert Committee noted Bioproject Pharma's brief response to the Subcommittee's earlier recommendation. Although the applicant had highlighted the existence of some additional information about exposure to racecadotril in the Safety Report, their response contained little in the way of new data. On these grounds, the Expert Committee decided that there is no basis to amend the recommendation made by the Subcommittee in July.

3.5 Review of other applications

The Expert Committee noted that the following applications for additions to the WHO Model List had not been recommended by the Subcommittee at its meeting in July, and that since then no comments from the applicants had been received:

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

At the present meeting, the Expert Committee endorsed the recommendations of the Subcommittee with respect to the above mentioned medicines.

3.6 Review of other comments on the provisional list

The Expert Committee reviewed a number of other proposals and comments that it had received on the Subcommittee's report and the provisional EMLc

that had been posted on the WHO web site. Comments had been received from:

- Health Action International
- The German Society of Paediatrics and Adolescent Medicine
- UNICEF Supply Division
- Dr Bruce Reidenberg, USA
- The Congenital Adrenal Hyperplasia Community
- Dr T.H. Tulchinsky, Israel
- Dr Madlen Gazarian, Australia
- Ms Jane Briggs, Management Sciences for Health, USA
- International Network for Rational Use of Drugs (INRUD), India

The comments were generally one of two types, either proposals regarding individual medicines or comments about general principles.

The Expert Committee noted that there was no clear consensus in the proposals relating to individual medicines. The German Society of Paediatrics and Adolescent Medicine had recommended several possible additions and various other changes, including the insertion of contraindications for specific medicines. Having undertaken a preliminary review of its proposals, the Secretariat encouraged the Society to submit some of them as formal applications for modifications to the EMLc. The Expert Committee thanked the Society for its extensive comments and looked forward to receiving fuller proposals.

Particular note was taken of the concerns that were expressed by several commentators about the use of ceftriaxone in neonates and premature babies. The Expert Committee decided to recommend a review of safety in these population groups, and to amend the EMLc to include an R (review) symbol for this medicine.

The Expert Committee noted with interest the commentary from Dr Tulchinsky on vitamin K. Since the dosage forms that were on the list were considered appropriate for neonates, the Committee concluded that no further modification was required at this time.

The Expert Committee then considered some of the more general comments that had been made. The criteria for essential medicines in children had been agreed to be the same as those in adults, which are based on public health need, comparative effectiveness, safety and cost-effectiveness.

The Expert Committee noted comments about the appropriateness or otherwise of using registration/licensing by a competent authority as a

proxy for detailed evidence of effectiveness and safety. On reflection, it considered that for the first EMLc this practice was acceptable.

The Expert Committee also noted that for some "core" adult medicines, specialist facilities or experience would clearly be required when used in children (e.g. medicines for heart disease). However, it was apparent that the reason for listing some medicines as "complementary" for children but as "core" for adults was not always as obvious. Although any apparent inconsistencies could easily be managed when the two lists were separate, the Expert Committee acknowledged that these could lead to confusion if there was only one. As in the case of the square boxes (see Section 2), the Expert Committee decided to review potentially "discrepant" complementary medicines at its meeting in 2009, by which time further review work will have been completed.

The Expert Committee agreed with several commentators who had argued the case for greater consistency between the Model List and current WHO treatment guidelines. To this end, the Committee recalled the recent review of treatment guidelines that had been presented to the July Subcommittee meeting, which had indeed identified a long list of discrepancies (http://mednet3.who.int/EML/expcom/CHILDREN/Items/ReviewGuidelines.pdf). A key problem was differences between the *Pocketbook of Hospital Care for Children* and the Model List. In a number of cases, medicines recommended in the *Pocketbook* had recently been deleted from the Model List (based on a review of the evidence), necessitating a review of the recommendations given in the *Pocketbook*. However, for the majority of medicines, the differences are in the recommended dosage forms and strengths, though it was not always clear that revisions were required to the forms listed on the EML.

The Expert Committee agreed that no further action is needed with respect to Tables 2 and 3 of the WHO review. Discrepancies relating to Tables 4, 5 and 6 will be reviewed by the Secretariat and a revised list of medicines will be presented to the next meeting. WHO treatment guidelines and the recommendations contained in *Integrated Management of Childhood Illness* may also need to be updated in relation to new evidence, and in some instances, the Committee noted that WHO would need to develop new guidelines.

Other individual recommendations were acknowledged at the present meeting and considered. Some of the items are mentioned in the earlier item relating to research (see Annex 1*)*. Most require specific applications for addition to or deletion from the Model List. Such formal applications would be welcome.

4. Update on related activities

4.1 Report on preliminary work on neonates

The Expert Committee was briefed by the Secretariat about the outcome of some preliminary work on medicines for neonates, in particular, in relation to existing WHO treatment guidelines. Neonatal care had been considered at three levels: basic care, referral care and high-level care.

In terms of basic care, many of the medicines needed to deal with the most common problems in neonates are already on the Model List, although not all of them are listed in an appropriate dosage form and strength. The Secretariat proposed that, as its first priority, it would review the medicines needed for this level of care and ensure that the dosage forms and strengths were appropriate, and where necessary make recommendations to the Subcommittee about the additional forms needed. This was agreed by the Expert Committee.

For second- and third-level care, which would be provided in some but not all countries, the main clinical problems had been identified as:

- problems related to pre-maturity, such as respiratory problems (mechanical ventilation, lung maturation), necrotizing enterocolitis, apnea;
- cardiovascular problems, including for example, hypotension, duct-dependant cardiac anomalies;
- infections;
- asphyxia, hypoxic-ischaemic encephalopathy and meconium aspiration syndrome;
- pain relief and sedation;
- neonatal abstinence syndrome;
- metabolic disturbances and supplementations;
- managing intravenous access.

Medicines for treating some of these conditions and health problems are already on the Model List. However, for other problems (e.g. lung maturation) other medicines might need to be considered, such as surfactants. The Secretariat had identified a long list of other possible treatments.

Noting that neonatal intensive care units, or high-dependency second-level neonatal units, are not available in all countries, and that the burden of disease in critically ill or premature neonates is difficult to define, the Committee proposed that the Secretariat's next step should be to draft a list of neonatal health problems and related medicines, to include information about appropriate dosage forms and strengths as well as supporting evidence for their use.

The Expert Committee recommended that the Subcommittee should consider whether it would be appropriate to develop a separate section for neonatal medicines and if so, should this separate section be retained after the EMLc is merged with the Model List? The Expert Committee also asked the Subcommittee to further advise the Secretariat on how best to prioritize work in relation to this large and hitherto largely neglected area of work.

4.2 Report on research priorities

Ms Elin Haf Davies, Dr Dianne Terlouw, Dr Gregory Kearns and Dr Donald Mattison joined the Expert Committee for the discussion of this item.

The Expert Committee considered the report from the Informal Consultation on Research Priorities for Essential Medicines in Children (which is attached to this meeting report as Annex 1). The Expert Committee reminded participants that the children's list is a **supplement** to the Model List and not a **replacement**. Consequently, products such as radiocontrast agents, which are not currently specified on the list of children's medicines should not be seen to be precluded for use in children. Clearly, information was needed to inform the choice of radiocontrast medicines in children.

In addition to the research needs identified in the report, a number of other important knowledge gaps were highlighted and discussed, as follows:

- There is a need for a review of international controls governing medicines used in palliative care; this would allow ways of ensuring better access in situations of medical need, including use in children, to be identified.
- More research into malaria treatments, including FDCs that are appropriate for use in children, is urgently needed.
- Problems associated with access to insulin and hormonal preparations need to be resolved (the withdrawal of animal-derived insulins has led to a disruption in the supply of human-sequence insulin).
- Information on the supply of medicines that need special storage is generally lacking; in particular, studies investigating the effectiveness of the variety of local methods used for maintaining the cold chain and their impact on the stability of the product were needed. Although it was acknowledged that this is an issue that is not necessarily restricted to medicines for children.
- New methods are needed for identifying delayed adverse effects, especially effects on development in children.
- Medicine-related equipment, such as syringes, need to be made available in appropriate sizes for the full age range of patients.

- More needs to be known about the effects of, and treatments for, environmental pollutants, especially as growing children are more affected than adults. It was suggested that the Model List needs to include antidotes for environmental pollutants, in cases of both acute and chronic poisoning.
- Much more needs to be known about the factors that modify dose-response relationships in individuals and populations.

Conclusion

The Expert Committee thanked the Subcommittee for the comprehensive review of essential medicines for children. It recommended that the provisional list should be endorsed as the first WHO Model List of Essential Medicines for Children. Noting the numerous gaps and needs for research and reviews, the Expert Committee recommended that the Subcommittee should meet again in approximately 12 months to further review the list for consideration at the next regular meeting of the Expert Committee in March 2009.

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Annex 1

Report of an Informal Consultation on Research Priorities for Children's Medicines, 2007

Informal Consultation on Research Priorities for Children's Medicines

Geneva, 23 October 2007

Members

Professor Noël Cranswick, Royal Children's Hospital/Australian Pediatric Pharmacology Research Unit, Parkville, Victoria, Australia

Mr Andy Gray, Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Congella**,** South Africa

Dr Kalle Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland

Dr Marcus Reidenberg, Chief, Division of Clinical Pharmacology, Weill Medical College, Cornell University, New York, NY, USA

Temporary advisers

Dr Pisonthi Chongtrakul, Thai Board of Pediatrics, Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Ms Elin Haf Davies, Scientific Coordinator, European Medicines Agency, London, England

Dr Gregory Kearns, Professor of Pediatrics and Pharmacology, University of Missouri, Kansas City, MO, USA

Dr Donald Mattison, Senior Advisor to the Directors of the National Institute of Child Health and Human Development and the Center for Research for Mothers and Children, and Branch Chief, Obstetric and Pediatric Pharmacology Branch, National Institutes of Health, Rockville, MD, USA

Dr Hidefumi Nakamura, Director of Clinical Research, National Children's Medical Centre, National Centre for Child Health and Development, Tokyo, Japan

Dr Jane Robertson, Senior Lecturer, Department of Clinical Pharmacology, University of Newcastle, Australia

Dr Dianne Terlouw, Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Liverpool, England

Dr Li Zhiping, Director, Department of Pharmacy, Children's Hospital of Fudan University, Shanghai, People's Republic of China

Secretariat

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

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

Dr Suzanne Hill, Scientist, Policy, Access and Rational Use/Medicines Policy and Standards, WHO, Geneva, Switzerland (*Secretary*)

Dr Elizabeta Zisovska, Policy, Access and Rational Use/Medicines Policy and Standards, WHO, Geneva, Switzerland

1. Introduction

An informal consultation meeting was held in Geneva on 23 October 2007 to discuss strategies for setting priorities for research into children's medicines. The meeting had been convened in response to a request from the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines for assistance in formulating research priorities, given the numerous knowledge gaps it had identified during the course of the development of a provisional list of essential medicines for use in children. In preparation for the meeting, the Secretariat had conducted a survey of paediatricians, pharmacologists and Expert Committee members in order to begin the process of priority setting given the extensive list of research topics the Subcommittee had identified.

Dr Hans Hogerzeil welcomed the participants to the meeting and commented that he hoped that the discussions would lead to some innovative thinking to guide research and progress matters in relation to medicines for children. Dr Clive Ondari asked the members to bear in mind, throughout the course of their deliberations, the importance of getting medicines to where they are most needed, notably in primary care. In particular, the group was encouraged to consider supply chain management issues, for example, market size and funding (i.e. how best to fund medicines to ensure that they are available and affordable to patients and their families). The group was also asked to provide guidance on approaches to improving prescribing practices and the administration of medicines so that improved health outcomes are realized.

Dr Suzanne Hill reminded the group of the need to focus on identifying information that would enable the Subcommittee to make informed decisions about applications to list specific drugs on the essential medicines list for children. She also asked participants to consider, in the absence of WHO funding for research initiatives, ways in which the research agenda might be carried forward, i.e. research institutions and funding strategies. The group was encouraged to think about how the work could be formulated as a global research agenda for children's medicines.

The group discussed the broad range of issues it felt should be considered. It was agreed that the scientific basis for research questions and the focus of interest need to be clearly articulated to the international research community in order to ensure clarity and also to maximize the usefulness of the information gathered. Similarly, it was important to recognize existing research infrastructure and capabilities; in this regard in particular, the group acknowledged a role for WHO in providing education and training to support high-quality research. It was recognized that while the needs of

developing and developed countries often differ, there are some research questions that are of global importance. Researchers should be encouraged to recognize needs beyond their own country boundaries, and that output of their research may make the greatest difference in areas not close to home.

Country-level reluctance to undertake trials in children was identified as a potential problem. The group identified another key role for WHO, namely, in promoting the moral imperative for gaining the new knowledge needed by studying medicine use in children. The need to promote further development in the formulation of paediatric medicines, both in general and in relation to specific medicines, was also raised. This work would include the provision of guidance on (a) priority formulations according to disease burden, (b) the formulation development process, and (c) the preparation of applications for adding medicines to the essential medicines list.

The group discussed the several ways in which prioritization of the research agenda could be organized or conceptualized — by using the priorities identified in the pre-meeting survey, by methodological issues (i.e. study design), by topic area (e.g. respiratory disease, TB, anti-infectives) or by burden of disease. After some reflection, the group agreed that the diverse research agenda could be considered in three categories:

1. Highly feasible work that could be undertaken using existing evidence and be completed in reasonable time to inform decisions by the Subcommittee in 2008;
2. Work that after preliminary review of the evidence was likely to require additional studies, such as modelling studies or bridging pharmacokinetic studies;
3. Research questions where issues of study design and quality were important and there was likely to be a need for research infrastructure support and training.

This framework was adopted to guide the subsequent discussions of the group.

2. The research agenda

2.1 Highly feasible work

This category of research activity tends to be related to medicines where there is evidence of efficacy and safety and some experience with use in children. Consequently, the work required largely involves systematic review of the existing evidence base.

The meeting identified the following (in order of priority) as being highly feasible research questions or reviews: (the current priority score was used as the basis for assigning priorities):

- review of the age limits and safety data for use of antihelminths in children;
- review of the age limits and safety data for use of antitrematode medicines in children;
- review of the choice of oral cephalosporins and the choice of a suitable antipseudomonal cephalosporin;
- use of rifabutin and rifapentin in children with TB co-infection in HIV;
- the choice of medicines in respiratory disease, including:
  - use of ipratropium and long-acting beta agonists;
  - the efficacy of oral salbutamol preparations (beyond the scientific question, the group recognized that there is a policy and practice dimension that would also need to be addressed);
- use of antidotes in children;
- commence evaluation of essential oncology medicines for children;
- the choice of macrolides in children (the group identified several aspects to this research question — comparative safety and efficacy of macrolides, if erythromycin is used which salt? use in neonates);
- use of fluoroquinolones in children (the group focused the research to a review of the toxicity of fluoroquinolones, including in relation to benefit);
- use of diazepam and alternatives such as midazolam in children;
- use of ibuprofen;
- review of anticonvulsants, particularly newer agents;
- role of intravenous sodium valproate for status epilepticus;
- the choice of laxatives in children.

The meeting also considered a range of possible partners and likely funding sources. The following organizations were identified (in no particular order):

- the International Collaboration for Child Health Research;
- the National Institute for Child Health and Human Development;
- BMJ Clinical Evidence;
- the International Programme on Chemical Safety;
- the University of Liverpool (Tropical Diseases);
- organizations interested in promoting rational use of antibiotics.

Recognizing the importance of making the research agenda broadly known to industry and researchers, the meeting supported a proposal to submit a commentary for publication to flag priority research areas. It considered

that while there should be a broad invitation to interested parties to address any of the questions raised by the Subcommittee, the emphasis should be on research questions that relate to the global burden of disease list used by WHO and the World Bank. The group also recognized the importance of providing clear guidance on the processes of preparing applications for consideration by the Expert Committee on the Selection and Use of Essential Medicines.

2.2 Study design

Ethical issues

The process of developing a list of essential medicines for use in children has highlighted significant gaps in the knowledge base which supports rational decisions about the selection of the best medicines for use in children. Clearly, these knowledge gaps need to be filled by research that requires that clinical trials be carried out in children. However, in many settings, there are barriers to conducting studies in which the subjects are children.

The present meeting recommended that the Expert Committee on the Selection and Use of Essential Medicines ask the Subcommittee to address the ethical issues relating to research in children. Recognizing the moral imperative to gain the new knowledge needed by conducting studies in children — so that medicine use in these populations is safe and effective — the group also recommended that the Subcommittee be requested to prepare a position paper over the next year and to commission work to bring together evidence that already exists in a number of jurisdictions on the conduct of trials in children. The resulting documentation should be posted on the web and comments invited. Any new ethical issues that are not addressed in the reference documents, should be brought to the attention of the Secretariat.

Methodological issues

The nature of studies required will depend on the medicine being considered. In cases where bridging pharmacokinetic studies would be appropriate, the group acknowledged that there is a very real need to make the methods of conducting these types of studies much more widely known. The linking of individuals and research institutions that perform such studies was considered to be an important step forwards in the realization of this objective.

The group was unable to recommend a standard pathway for conducting specific types of studies at the present time. It therefore recommended that specific diseases and/or medicines be used to develop these approaches,

and that as TB, malaria and neglected tropical diseases had been identified as priority questions for the EMLc, these could be used as the initial examples.

Education and capacity building

The group acknowledged the need to disseminate more widely, detailed information on appropriate study designs and on the relative merits of the different approaches to evaluating the effectiveness and safety of medicines. A key concern was that any research conducted needed to be of high quality and reported in a format that was consistent with accepted standards, such as the CONSORT statement for RCTs (http://www.consort-statement.org/). The group identified the need for standardized reporting of pharmacokinetic studies and requested that groups such as IUPHAR consider the development of reporting standards.

WHO was perceived to have a pivotal role in the linking of experienced and less experienced researchers and in facilitating the translation of research methods from developed to developing country settings. However, the group considered that greater coordination within WHO (to identify research activities already being undertaken by groups such as TDR) was needed to ensure there is no duplication of effort. It was also suggested that WHO should assume a role in coordinating and encouraging the development of educational programmes that build capacity to undertake clinical trials in children.

2.3 Dosage forms and excipients

It was proposed that a brainstorming meeting to discuss innovation in paediatric dosage forms be convened. The Expert Committee on Pharmaceutical Specifications and the WHO Department of Quality Assurance and Safety: Medicines (QSM) should be invited to participate in discussions about what is feasible in terms of development of new dosage forms and strengths for specific drugs.

The group also recommended that the Expert Committee on the Selection and Use of Essential Medicines request the Subcommittee to identify priority drugs for the treatment of HIV, TB, malaria, pneumonia and diarrhoea in children, bearing in mind that liquid dosage forms are suitable for children aged under 3 months and oral dosage forms are required for children aged over 3 months. Possible child-friendly dosage forms discussed by the group included scored tablets (provided with a tablet cutter), lower-strength tablets or mini-tablets, sachets for reconstitution, unit dose powders, inhalers (with spacers and substitute devices that

can be made and used by families) and chewable tablets. The need for information on the stability of medicines when mixed with yoghurt or other foodstuffs was also mentioned.

2.4 Regulatory issues

The group recognized that although some jurisdictions have provided incentives for the conduct of paediatric studies, elsewhere regulatory barriers limit not only clinical trials in children but also access to medicines for children. The barriers include:

- inappropriate restrictions on performing studies in children;
- lack of regulatory guidelines and mechanisms to encourage registration of medicines for children;
- lack of good quality evidence to support updating dossiers or indications, particularly for older medicines;
- lack of capacity within countries to assess applications for medicines for children.

The group recommended that WHO work with regulatory authorities who have in place structures that permit studies in children to identify which regulatory guidance can be most readily adapted for global use. It was also suggested that WHO should consider ways of providing in-country support and education and training in regulatory issues and approval processes for clinical trials in children. Standard methods for pharmacovigilance in children would also need to be developed. However, the group recognized that there may be differences in the data requirements of regulatory authorities and in the evidence deemed sufficient to answer academic questions.

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Annex 2

First Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines

Geneva, 9-13 July 2007

Members

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

Dr Helena Lutescia L. Coelho, Pharmacy Department, Federal University of Ceara, Fortaleza, Brazil

Professor Noël Cranswick, Clinical Pharmacologist, Royal Children's Hospital/Australian Paediatric Pharmacology Research Unit, Parkville, Victoria, Australia

Mr Andy Gray, Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa

Professor Prakash Mohan Jeena, Department of Paediatrics and Child Health, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, South Africa

Dr Kalle Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland

Dr Peter Kazembe, Baylor College of Medicine, Children's Clinical Centre of Excellence, Lilongwe, Malawi

Temporary advisers

Professor Dai Yao Hua, Director, WHO Collaborating Centre for Child Health, Capital Institute of Paediatrics, Beijing, People's Republic of China

Dr Gregory L. Kearns, Professor of Paediatrics and Pharmacology, University of Missouri Kansas City, Director of Medical Research, Children's Mercy Hospital and Clinics, (UMKC), Kansas City, MO, USA

Dr Sverre Lie, Department of Paediatrics, International Paediatrics Association (IPA), Rikshospitalet, 0027 Oslo, Norway

Dr Stuart MacLeod, Executive Director, Child & Family Research Institute, Children's & Women's Health Centre of British Columbia, Ambulatory Care Building, Vancouver, Canada

Dr Robert G. Peterson, Clinical Professor, Department of Pediatrics, University of British Columbia, Vancouver, Canada

Dr Shalini Sri Ranganathan, Senior Lecturer in Pharmacology & Consultant Paediatrician, Department of Pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka

Dr William Rodriguez, Food and Drug Administration, FDA/CDER/OND, Rockville, USA

Professor H. P. S. Sachdev, Senior Consultant, Paediatrics and Clinical, Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi, India

Dr Anita Zaidi, Associate Professor, Department of Paediatrics and Microbiology, Aga Khan University, Karachi, Pakistan

Intergovernmental organizations

Mrs Hanne Bak Pedersen, Deputy Director, UNICEF Supply Division, Copenhagen Freeport, Copenhagen

Secretariat

Dr Krisantha Weerasuriya, Regional Adviser, Essential Drugs and Medicines Policy, WHO Regional Office for South-East Asia

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

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

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

1. Introduction

The WHO First Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines met in Geneva from 9 to 13 July 2007. The meeting was opened on behalf of the Director-General by Dr Howard Zucker, Assistant Director-General for Health Technology and Pharmaceuticals. He stated that WHO's medicines programme is very important to Member States and that the recommendations made by its Expert Committees are critical. This new Subcommittee of the Expert Committee was approved by the Executive Board in May 2007 (EB121. R2), specifically to advise on essential medicines for children, as shown below:

> *"The Executive Board,*
> *Having considered the report by the Secretariat on the establishment of a Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines,*
>
> *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."*

This also followed from the WHA resolution on Better Medicines for Children (WHA60.20) which requested the Director-General to:

(1) promote the development, harmonization and use of standards for clinical trials of medicines for children; to revise and regularly update the Model List of Essential Medicines in order to include missing essential medicines for children, using evidence-based clinical guidelines; and to promote application of such guidelines by Member States and international financing bodies, with initial focus on treatments for HIV/AIDS, tuberculosis, malaria and chronic diseases;

(2) ensure that all relevant WHO programmes, including but not limited to those on essential medicines, contribute to making safe and effective medicines as widely available for children as for adults;

(3) promote the development of international norms and standards for quality and safety of formulations for children, and of the regulatory capacity to apply them;

(4) make available evidence-based treatment guidelines and independent information on dosage and safety aspects of essential medicines for children, progressively to cover all medicines for children, and to work with Member States in order to implement such guidelines;

(5) collaborate with governments, other organizations of the United Nations system, including WTO and WIPO, donor agencies, nongovernmental organizations and the pharmaceutical industry in order to encourage fair trade in safe and effective medicines for children and adequate financing for securing better access to medicines for children;

(6) report to the Sixty-second World Health Assembly, and subsequently as appropriate, through the Executive Board, on progress achieved, problems encountered and specific actions needed to further promote better access to medicines for children.

Dr Zucker briefly explained some aspects of the procedures for Expert Committees to members of the Subcommittee. He stated that the Subcommittee is not a representative one, that all members participate in their personal capacity and are not allowed to take instructions from any government or any other authority. (See Appendix 1 for Committee Members' Declarations of Interest).

Prior to the Open Session, Dr Clive Ondari, Coordinator, Policy, Access and Rational Use of Medicines Team, addressed the Committee. He noted that this new Subcommittee represented a very important contribution to the programme of work on Better Medicines for Children.

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 draft WHO Model List of Essential Medicines for Children (EMLc). Furthermore, for Subcommittee members it provided an opportunity to receive, at first-hand, additional information and opinion on matters under consideration. Discussions and considerations of the open session are reflected in the report of the meeting.

The Subcommittee decided to adopt the report format used by the Expert Committee. A summary of the Subcommittee's considerations on each of the items under discussion is presented in the main body of the report. The discussion on research gaps is presented in Section 5, together with a list of dosage forms needed for children. The List is presented as Appendix 2. The Anatomical Therapeutic Chemical (ATC) classification system as Appendix 3; and a list of items on the Model List ordered by their corresponding ATC classification code number(s) is included as Appendix 4.

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, and are accessible through the Essential Medicines Library (http://www.who.int/emlib).

2. Open session

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

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

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

Dr Suzanne Hill provided background to the meeting, explained the WHO rules governing Committee processes and identified the expected outcomes of the Subcommittee meeting. In addition to the first EML for children and a report of the Subcommittee deliberations, it is expected that the Subcommittee will make recommendations about dose forms, identify additional information needs and research gaps, and make recommendations about timelines and next steps to advance the agenda for better medicines for children.

In response, Professor Cranswick, Dr Rodriguez, Dr Peterson, Professor Sachdev and Professor Jeena commented on the relationship between the existing EML and the EML for children. They noted the importance of not creating confusion for countries or procurement agencies; the need to assess the effectiveness of the EML process and uptake at the country level; assessing disease burden and its influence on drug selection (recognizing that some diseases posed a heavy burden but only in selected settings); and issues regarding assuring the availability of medicines.

Professor Cranswick provided a summary of two reviews conducted to identify gaps in the availability of paediatric medicines. The reviews were based on existing 2003 and 2005 EMLs and sought to identify medicines for which there were paediatric indications for use and that were not on the current EML. Where a paediatric formulation was available in the USA, UK or Australia, there was an opportunity for inclusion in the EML; where medicines were not available in a suitable paediatric dose form, these could be the basis of a list to prioritize pharmaceutical development needs. Professor Cranswick urged a comprehensive review of WHO practice guidelines to ensure that there was consistency between the EML and treatment guidelines.

Mrs Hanne Bak Pedersen (UNICEF) provided a user perspective on the role of the EML, focusing particularly on the issue of quality of medicines. Mrs Bak Pedersen highlighted the variance in medicines regulation and good manufacturing practices (GMP), and stressed the importance of prequalification of medicines. She noted that in order to improve access to quality medicines, consistent messages, about quality requirements in relation to procurement of medicines, should come from all partners involved; for example, organizations setting standards and providing guidelines, financing structures, procurement agencies, manufacturers, national regulatory authorities. In response to several questions about the activities of UNICEF, Mrs Bak Pedersen described UNICEF's role in supporting innovation for children and facilitating coverage with new medicines in support of child health, e.g. artemisinin-based combination therapies and zinc tablets.

Dr Martin Weber (Department of Child and Adolescent Health) and Dr Siobhan Crowley (HIV Department) of WHO spoke of the contribution of the EML for children in supporting the work of the two departments. Dr Weber spoke of the importance of guidelines to support the EML and influence prescribing practices. Dr Crowley spoke of the particular issues relevant to HIV medicines for children, highlighting the importance of appropriate fixed-dose combinations in programme delivery and improving access to HIV medicines, which will be required life-long by affected children.

Dr Myriam Henkens and Dr Fernando Pascual of Médecins Sans Frontières International spoke in support of the development of the EML for children and emphasized the importance of the two lists (EML and EML for children) working in concert and avoiding confusion at the country level. MSF offered specific comments on a number of medicines to be considered by the Subcommittee (oily chloramphenicol injection, vaccines, fixed-dose combinations for malaria and HIV and preferred dosage forms).

Dr Smiljana Ristic (Hoffman La Roche) spoke of the company's commitment to work in the area of paediatric medicines and to consider paediatric products early in the product development cycle. In response, Dr Peterson asked whether there was progress in collaborative work between pharmaceutical manufacturers, to collectively develop clinical trials methods applicable to paediatric medicines as a non-competitive process. In response, Dr Detlef Niese (Novartis) identified the role of initiatives such as the EU Framework 7 in supporting the work of development of paediatric medicines and as a mechanism to fill some of the gaps identified.

Dr Macleod, Dr Hoppu and Dr Jeena sought further comments on the activities of UNICEF, and encouraged the organization to be more proactive in its engagement with the pharmaceutical industry, and to advocate for paediatric research. Dr Jeena emphasized the importance of moving beyond the EML and advocated a role for UNICEF and WHO as stewards to make the EML work at country level.

3. Policy items

3.1 Criteria for the selection of essential medicines for children

The Subcommittee considered the existing criteria for the selection of essential medicines, approved in 2001 by the Executive Board of the World Health Assembly. These criteria are listed below.

1. The choice of essential medicines depends on several factors, including the disease burden and sound and adequate data

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

2. Most essential medicines should be formulated as single compounds. Fixed-ratio combination products are selected only when the combination has a proven advantage in therapeutic effect, safety or compliance over single compounds administered separately. Examples of combination medicines that have met these criteria include new formulations for tuberculosis and malaria.

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

The Subcommittee noted the comments from the WHO Department of HIV:

> *"Pharmacokinetic (PK) and pharmacodynamic considerations are very different and mean that formulations suited to adults may not always be most appropriate, or contain proportions of active pharmaceutical ingredients best suited to dosing in children. The need for medicines to be given by care givers for younger children, and to children who may be unable to swallow solid forms, to tolerate alcohol excipient, or large volumes of some preparations based on age (e.g. 10 ml per dose is too much for a neonate) means specific products may be preferred for the paediatric population, and should be reflected in criteria for inclusion for children medicines."*

The Subcommittee considered that the matter of appropriate dosage forms and strengths of medicines for children is included in criterion 1. The burden of disease in children may be different from that in adults but is still identified

as a criterion. The Subcommittee therefore accepted that these criteria were appropriate for selection of medicines for children, but decided to explicitly note consideration of dosage forms in its decisions. Specific consideration needs to be given to subgroups within the paediatric age range. Groups such as neonates and premature neonates, whose disease burden may make them therapeutic orphans even within the paediatric age range, need their unique therapeutic needs addressed. Every effort was made to include appropriate therapies for this age group.

The criteria for including an individual medicine on the list are in accordance with criteria 1, 2 and 3. However with respect to cost-effectiveness data, the Subcommittee was only able to consider acquisition costs.

For this first meeting, the Subcommittee decided that the list of medicines it selected would reflect the needs of children under 12 years of age. The Subcommittee acknowledged the need to consider medicines needs of adolescents, but as children aged 12-18 can generally use dosage forms of products that are designed for adults, it was decided to identify important essential medicines and dosage forms for children of under 12 years first. It was also decided to identify needs and gaps for research.

In view of the limited availability of paediatric data on medicines generally, the Subcommittee discussed the interpretation of a requirement for adequate data on efficacy and safety (criteria 1, 2 and 3), which would have to be assessed for all relevant age ranges below 12 years of age. It was to be expected that for many medicines such data would not be available for all paediatric age ranges, especially not for newborns. When considering medicines on the current EML, licensing by a recognized competent authority was considered to generally fulfil the criteria of adequate data on efficacy and safety within the age range of the market authorization. In the age range where a medicine was not licensed, or when there was no paediatric authorization at all, the medicine would be considered not to fill the criteria of adequate data on efficacy and safety, unless such data were made available for the Subcommittee.

At the end of the meeting, the Subcommittee reflected upon their experience of applying these criteria to the list in order to produce the first edition of the Essential Medicines List for Children. The following points were agreed:

- It was not possible to make a decision on as many medicines, some of them widely used, as the Subcommittee would have liked, because of non-availability of data in children to decide on criteria 1-3 required for inclusion on the EML.

- Data on disease burden in children was only exceptionally available for different paediatric age groups, so generally all children under 12 were considered together.
- The Subcommittee included paediatric oral liquid dosage forms for severe diseases, if available, even in cases where it was possible that the disease burden for the indication in very young children was lower than in older children, so as not to exclude them from treatment.
- Decisions regarding adequate data on efficacy and safety in children have generally to be made on the basis of approval of a medicine in a country with a well recognized regulatory system. The age restrictions identified usually reflect lack of licensing in the age range. However, it was difficult to determine the licensing status of many medicines in children, so as additional information on the licensing status of these medicines becomes available, the age range can be extended, and some of the medicines pending endorsement can be included.
- Information on formulations suitable to cover the needs of children of all age ranges was often difficult to find. If additional information on existing formulations becomes available these may be added.
- When additional information on licensed, age-appropriate formulations for all age groups becomes available, it may be possible to extend the current age limits.
- The Subcommittee retained the current structure of the list but identified a number of Sections that needed further refinement to allow for inclusion of age-related information and specific indications. For this edition, items with age restrictions on use are marked with an [a] and items endorsed but identified for review are marked with an [R].

3.2 Criteria for selection of fixed-dose combination products

The Subcommittee considered the Expert Committee Report of the discussion in March 2007 on selection of fixed-dose combination (FDC) products and decided that the same consideration would apply to selection of FDCs for children (see WHO Technical Report Series No. 929, WHO Expert Committee on Specifications for Pharmaceutical Preparations). However, the Subcommittee noted in particular the importance of defining the strength of components in FDCs for children in such a way as to ensure that the products could be used by as many different age groups (or weight band groups) of children as possible, particularly in the context of treatment of chronic disease where simplified dosing schedules are desirable to enhance adherence. Members noted that there may be a specific need for FDCs for the treatment of malnutrition, TB, malaria and HIV in children. However, it would be necessary to have sufficient evidence to show that the

strength of all the components in a FDC was such that it would not lead to underdosing with consequent risk of treatment failure and development of resistance, or overdosing with toxicity due to different developmental pharmacology of the individual components across an age range. The Subcommittee noted that this special challenge, in contrast to adults, was not specifically addressed in the WHO Technical Report Series No. 929.

3.3 Paediatric age categories

The Subcommittee considered the background paper prepared by the International Pharmaceutical Federation (FIP) and the comments received from experts. The Subcommittee particularly noted the comments from the WHO Department of Child and Adolescent Health which suggest that the proposed draft from FIP was not consistent with international standards and WHO definitions. The Subcommittee also considered regulatory age categories recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (http://www.ich.org/).

While acknowledging the above contributions, the Subcommittee decided not to restrict itself to any standard paediatric age categories but stated the following:

- The age range of any particular medicine will be dependent upon its particular pharmacokinetic and pharmacodynamic ontogeny.
- Dosing considerations will depend upon developmental age and weight considerations (e.g. liquid versus chewable tablet).

It was recognized that development is a continuous process, and that any age categorization is arbitrary. Recommendations for individual medicines may not link directly to the developmental categories. For the purposes of the selection of medicines for the Essential Medicines List for Children (EMLc), the age categories will largely depend upon the available data for efficacy and safety. This would be most likely to follow the ICH age categories. In developing this list, the committee mainly considered the inclusion of appropriate dosage forms for neonates and young children.

3.4 Preferred dosage forms

The Subcommittee considered the draft position paper prepared by FIP and also the comments from Médecins Sans Frontières (MSF) and Professor Tony Nunn. Mindful of the need for practical solutions to the problems of delivering dosage forms in a variety of settings, the Subcommittee

recommended that there is an urgent need for dosage forms that are better suited to meeting the needs of children in a variety of different settings. In considering currently available dosage forms, the Subcommittee noted that the preferred oral form in children will depend upon age and developmental level. Young children will need a liquid form to ingest, while older children will be able to swallow solid dose forms. The actual age at which a solid dose form can be ingested will depend upon the size of the tablet and its palatability. Chewable or crushable forms may be acceptable at a younger age. The Subcommittee considered whether it could recommend a minimum age for use of oral solid dosage forms as opposed to liquid forms but decided that without a review of the evidence it was not able to do so at this time.

Overall, the Subcommittee discussed available dosage forms and noted many deficiencies. It strongly recommended the development of new, innovative and affordable developmentally appropriate dosage forms. This will avoid the inappropriate practice of dividing adult dosage forms, with the resultant risk of inappropriate dosing in children. The Subcommittee also noted the need for measuring devices for dosing children.

3.5 Position paper on off-label use

The Subcommittee considered the draft position paper on 'off-label' use of medicines in children. It noted in particular the finding that there is very little information about the extent of off-label use in developing countries and also noted the substantial risk associated with the use of unregistered medicines in children. Given that there appears to be a relationship between off-label use and morbidity from adverse reactions, the Subcommittee recommended undertaking studies on the extent of off-label use in children. The Subcommittee also noted the various categories of off-label use proposed in the document and considered that this approach offered a helpful framework for assessing benefits and harms of potential off-label use in children. One of the challenges is to encourage appropriate conduct of clinical trials in children and this was also considered in the context of the review of regulatory activities (see below). The Subcommittee suggested the following actions should be taken by WHO:

- Identify key areas in children's medicines where off-label use is prominent and problematic;
- Develop an appropriate formulary for children;
- Identify appropriate formulations for children;
- Encourage assessment of existing data and, where appropriate, additional clinical trials in the treatment of children in areas where there is insufficient evidence to guide prescribing;

- Promote pharmacovigilance to monitor medicines when off-label use is common.

3.6 Review of adherence

The Subcommittee noted the review.

3.7 Review of regulatory activities

The Subcommittee considered the summary of regulatory activities and also expressed concern about the widespread availability of substandard and counterfeit medicines in many countries.

The Subcommittee recommended that a more extensive review of regulatory approaches be undertaken and used as the basis for discussion of the development of a standard approach for countries to adopt to encourage registration of medicines for children. The Subcommittee identified the urgent need for new approaches to encourage development and regulatory approval of medicines for children, as the current market exclusivity incentives are insufficient to encourage the registration of medicines for children in all settings.

4. The WHO Model List of Essential Medicines for Children — by Section

Section 1. Anaesthetics

Anaesthetics have been on the Model List of Essential Medicines since the first edition in 1977 and are clearly also relevant as essential medicines for children.

The Section currently has three subsections and lists:

1.1 General anaesthetics and oxygen: ☐ halothane, ketamine, nitrous oxide, oxygen, ☐ thiopental.

1.2 Local anaesthetics: ☐ bupivacaine, ☐ lidocaine, lidocaine + epinephrine (and ephedrine on the ***Complementary List*** for spinal anaesthesia during delivery).

1.3 Preoperative medication and sedation for short-term procedures: atropine, ☐ diazepam, morphine, promethazine.

Reviews of this Section were prepared by Dr Peterson and Dr Coelho. The list of those providing comments is in Appendix 6. No applications for additional medicines for this Section were submitted.

The Subcommittee noted that all of these medicines have been licensed for use in children for either these, or related indications. However, the following specific comments were also noted:

- in some countries, halothane was no longer used and alternative inhalational anaesthetics such as sevoflurane were preferred. Halothane is retained in the current list but should be reviewed for the next meeting in 2008.
- that ketamine is a very useful anaesthetic agent in children. Concern about its central nervous system adverse effects was noted.
- the declining use of atropine preoperatively in some countries.
- the potential for use of midazolam as an alternative to diazepam.
- that promethazine is contraindicated for use in children under 2 years, due to the risk of respiratory depression. Promethazine was not reviewed for the current meeting and therefore not endorsed and should be reviewed for the next meeting in 2008.
- the need to develop an appropriate dosage form and strength of morphine for use in neonates and infants. The substantive risk of overdose was noted with the current dosage form and requires immediate attention. There should be a review of this category for the next meeting in 2008.

The Subcommittee therefore recommended that:

- nitrous oxide, oxygen, thiopental, halothane and ketamine be endorsed as essential medicines (as currently listed in the 15th EML) for children, but that thiopental should be listed without a square box, and that an application for sevoflurane or an alternative should be sought for the next meeting.
- bupivacaine, lidocaine, lidocaine + epinephrine should be endorsed as essential and that ephedrine should not be included in the EMLc.
- atropine, diazepam and morphine should be endorsed as essential but that the use of atropine preoperatively should be reviewed, and an application for midazolam should be sought. The Subcommittee also suggested that a lower concentration preparation of morphine injection would be appropriate.
- promethazine be reviewed and considered at the meeting in 2008.

Section 2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMS), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDS)

Section 2 of the 15th Model List of Essential Medicines has four sub-sections:

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs): acetylsalicylic acid, ibuprofen, paracetamol.

2.2 Opioid analgesics: codeine, morphine.

2.3 Medicines used to treat gout: allopurinol.

2.4 Disease modifying agents used in rheumatoid disorders: chloroquine. ***Complementary List:*** *azothiaprine, methotrexate, penicillamine, sulfasalazine*.

Reviews of this Section were prepared by Dr Coelho and Dr Peterson. Comments were received as listed in Appendix 6. No applications for additional medicines for this Section were submitted.

For Sections 2.1 and 2.2, the Subcommittee agreed that the management of pain in children is clearly an essential clinical need. The Subcommittee noted that aspirin is not recommended for use in children under 16 years in many settings and also recognized it had only a limited role, if any in the management of inflammatory conditions in children. It was recommended that aspirin be moved to the Complementary List, only for the management of rheumatic fever, juvenile arthritis and Kawasaki disease. Ibuprofen and paracetamol are both approved for use in children and there is extensive experience with both medicines. The question of inclusion of ibuprofen syrup was considered and the Subcommittee recommended that it should not be added without a full application with updated data being submitted. Therefore the Subcommittee recommended that ibuprofen and paracetamol as currently listed be endorsed as essential medicines for children.

For opioid analgesics, the Subcommittee endorsed morphine as essential and suggested that the dosage forms currently listed were appropriate, with the caveat that an age-appropriate dosing form for intravenous morphine be developed. The Subcommittee noted the uncertainty regarding the comparative effectiveness and safety of codeine, as well as the lack of efficacy of codeine in poor metabolisers and the potential of newer analgesics to replace codeine. A review of the use of tramadol in children was recommended.

The Subcommittee agreed that gout was not a paediatric disorder and therefore this Section was not relevant for the EMLc. However allopurinol was thought necessary for management of children within oncology practice and should be moved to that Section of the list. The role of DMARDs in the management of juvenile arthritis was acknowledged. The Subcommittee noted the comments from Dr Gazarian regarding relative prevalence and incidence of juvenile arthritis compared to epilepsy and diabetes in developed countries. It was therefore agreed that medicines for this disorder were potentially essential medicines for children, and that

evidence for the comparative effectiveness and safety of use of the currently listed products in children should be provided to the Subcommittee at its next meeting.

Section 3. Antiallergics and medicines used in anaphylaxis

The current listing in the 15th EML includes

3. **Antiallergics and medicines used in anaphylaxis:** □ chlorphenamine, dexamethasone, epinephrine, hydrocortisone, □ prednisolone.

Reviews of this Section were prepared by Dr Coelho and Dr Peterson. Comments were received as listed in Appendix 6. No applications for additional medicines for this Section were submitted.

The Subcommittee considered that allergic disorders (e.g. rhinitis, conjunctivitis, urticaria and contact dermatitis) are a common problem in children and therefore medicines for their treatment could be considered essential. Epinephrine was endorsed as essential for treatment of anaphylaxis. The question of inclusion of antihistamines was more difficult. The value of sedating versus non-sedating antihistamines needs to be assessed, and there are national preferences for particular medicines within these classes. Different dosage forms need to be available, and it was noted that if, for example, oral liquid forms of antihistamines were recommended, these might not be appropriate for use in children under 2 years.

In the absence of a formal review of comparative effectiveness and safety, the Subcommittee decided to endorse the inclusion of chlorphenamine injection, tablets and oral liquid with a square box on the Model List, noting that the choice of medicine within the class of sedating antihistamines would be a national one, depending upon availability and cost. The Subcommittee recommended that these medicines be reviewed as chlorphenamine is not registered for children under 1 year of age and may not be the best indicative drug for this class. The Subcommittee requested a review of diphenhydramine to assess the comparative efficacy and safety with chlorphenamine, as it may be applicable to a broader age range of children than chorphenamine. It also noted the need for a review of the use of non-sedating antihistamines in children for its next meeting.

The Subcommittee then considered the potential need for corticosteroids as listed in the Section. Dexamethasone was noted to be licensed (as the injection) for use in allergic disorders in children in some countries and is also used for non-allergic disorders, such as cerebral oedema, croup, post-

operative nausea and vomiting and in the treatment of bacterial meningitis. Hydrocortisone injection is licensed for use in hypersensitivity reactions, and prednisolone is licensed for 'steroid responsive' conditions.

While recognizing the need for systemic steroids in severe allergic reactions, the Subcommittee noted that for conditions such as allergic rhinitis and conjunctivitis, topical steroids or topical antihistamines have been shown to be effective and safer. The Subcommittee therefore recommended all three corticosteroids currently listed should be included on the Core List for children.

Section 4. Antidotes and other substances used in poisonings

The current listing in the 15th EML includes

4.1 **Non-specific:** charcoal, activated.

4.2 **Specific:** acetylcysteine, atropine, calcium gluconate, deferoxamine, dimercaprol, DL-methionine, methylthioninium chloride, naloxone, penicillamine, potassium ferric hexacyano-ferrate (II) -$2H_20$, sodium calcium edetate, sodium nitrite, sodium thiosulfate.

Section 4 of the Model List of Essential Medicines concerns medicines used as antidotes and for the management of poisonings. Comments were received as listed in Appendix 6. Reviews of this Section were prepared by Dr Coelho and Dr Peterson.

The Subcommittee noted that accidental poisoning with a variety of substances is a significant cause of morbidity and mortality in children in developing countries, particularly, for example, due to ingestion of unsafely stored pesticides. In the preliminary review, activated charcoal, listed as a non-specific antidote in Section 4.1 was identified as essential for children although not licensed in the sample of markets assessed. The Subcommittee considered that there was sufficient experience of use of activated charcoal in children to endorse it as essential.

In Section 4.2, acetylcysteine, atropine, calcium gluconate, deferoxamine, dimercaprol, sodium calcium edetate, naloxone and penicillamine were identified as licensed in children and potentially essential. Acetylcysteine was noted to be the preferred treatment for paracetamol poisoning and superior to DL-methionine. Atropine injection is used for organophosphate poisoning. All of these products were therefore endorsed as essential with the exception of DL-methionine that was not included in the EMLc and it was recommended that it be deleted from the main list.

Calcium gluconate was discussed for the treatment of poisoning (from plants containing oxalates, for example) and was endorsed as essential. Deferoxamine injection was endorsed as essential for use in iron poisoning and iron overload.

Dimercaprol, used in the treatment of heavy metal poisoning, was endorsed as essential. The Subcommittee noted that the reviewers questioned the comparative effectiveness and safety of methylthioninum chloride versus sodium nitrite for the treatment of methaemoglobinemia and therefore recommended that neither be endorsed as essential at this time without further review. Naloxone injection was endorsed as essential.

Lead poisoning was noted to be a significant public health problem in many developing countries and therefore treatment of lead poisoning was considered as essential to include on the EMLc. However, although penicillamine and sodium calcium edetate are licensed for this indication, there was no basis for the Subcommittee to determine which, if any was superior. The Subcommittee therefore decided to include both, but requested that a review of effectiveness and safety be carried out. The relevance of the treatment of thallium poisoning as requiring an essential medicine was unclear and therefore potassium ferric, which is not licensed in sampled markets for this indication was not included at this time. Sodium nitrite and sodium thiosulfate are both licensed for use in cyanide poisoning, but the clinical need for those medicines in children was not clear. The Subcommittee therefore recommended that the public health relevance of these products should be clarified before they are added to the EMLc. Overall, the Subcommittee recommended that the burden of disease and disability in children due to poisoning should be reviewed and used as the basis for a further revision to this Section of the EMLc at its next meeting. Specific consideration should be given to the treatment of organophosphate and lead poisoning in children, including applications for specific antidotes deemed critical for children (e.g. pralidoxime, obidoxime and dimercaptosuccinic acid).

Section 5. Anticonvulsants/antiepileptics

The current listing in the 15th EML includes

5. **Anticonvulsants/antiepilipetics:** carbamazepine, ☐ diazepam, magnesium sulfate, phenobarbital, phenytoin, valproic acid. ***Complementary List:*** ethosuximide.

In March 2007, the Expert Committee on Selection and Use of Essential Medicines reviewed a number of proposals for the addition of new dosage

forms of anticonvulsants for children. Section 5 therefore now includes carbamazepine (oral liquid, chewable and scored tablets), diazepam injection, magnesium sulfate injection, phenobarbital (injection, oral liquid and tablet), phenytoin (capsule, injection chewable and standard tablets and oral liquid), and valproic acid (oral liquid and crushable and enteric-coated tablet). Ethosuximide is included on the Complementary List as a capsule and oral liquid. The importance of the quality of the available products was emphasized.

Reviews of this Section were prepared by Professor Cranswick and Mr Gray.

The Subcommittee recommended that magnesium sulfate should not be included on the EMLc as its approved use is not relevant in children. Other comments regarding potential additions were also considered. The Committee requested that alternative benzodiazepines to diazepam (lorazepam and midazolam) be reviewed and the Subcommittee recommended that applications for these products should be submitted. The remaining list of medicines was endorsed as essential. The Subcommittee suggested a review of additional agents that may be useful in children, particularly intravenous valproate sodium, vigabatrin, gabapentin and lamotrigine.

Section 6. Anti-infective medicines

Section 6.1 Anthelminthics

The current listing in the 15th EML includes

6.1.1 Intestinal anthelminths: albendazole, levamisole, ☐ mebendazole, niclosamide, praziquantel, pyrantel.

6.1.2 Antifilarials: ivermectin. ***Complementary List:*** *diethylcarbamazine, suramin sodium*.

6.1.3 Antischistosomals and antitrematode medicines: praziquantel, triclabendazole, oxamniquine.

Reviews of these Sections were prepared by the Secretariat.

The Subcommittee noted that the WHO treatment guidelines for preventive chemotherapy in human helminthiasis include all medicines currently listed in Section 6.1 except suramin sodium. The safety of levamisole was reviewed in March 2007 by the Expert Committee and it was agreed to continue to include it, but to review it again in 2009 (or earlier, if new data become available). The current list of medicines in Section 6.1.1 was endorsed.

The Subcommittee questioned the need for suramin as a treatment of filariasis, given that the medicine of choice is ivermectin and alternatives are albendazole or diethylcarbamazine. Suramin sodium was not endorsed as essential and the Subcommittee recommended that the Expert Committee should also review the effectiveness and safety of suramin for filariasis in adults.

With regard to Section 6.1.3, the Subcommittee noted that generally praziquantel is the treatment of choice for these infections and is licensed for this indication. Triclabendazole is the treatment of choice for Fasciola infections, a significant neglected tropical disease. Although not licensed for use in children in high-income countries, there is some experience of use of it. Oxamniquine is recognized as second-line treatment. Noting that there are significant research gaps for medicines for children in this area, the Subcommittee decided to endorse these three products as essential but highlighted the need for adequate studies to determine the effectiveness and safety of these medicines in children.

The question of appropriate formulations of these medicines for children was also considered. It was noted, for example that mebendazole syrup is registered for use in some countries. However, the Subcommittee noted spontaneous reports of choking in association with the use of chewable formulations of albendazole, which highlighted that priority should be given to the development of dispersible tablet forms for children. A full review of this area is required for the next meeting.

Section 6.2 Antibacterials

6.2.1 *Beta Lactam medicines*

The current listing in the 15th EML includes: amoxicillin, amoxicillin + clavulanic acid, ampicillin, benzathine benzylpenicillin, benzylpenicillin, cefazolin, cefixime, ☐ cloxacillin, phenoxymethylpenicillin, procaine benzylpenicillin. ***Complementary List:*** *ceftazidime,* ☐ *ceftriaxone, imipenem* + *cilastatin*.

One of the major causes of morbidity and mortality in children is infections — pneumonia and neonatal sepsis are two of the most frequent causes of deaths in children under 5. The need for antibiotics to treat these infections therefore clearly satisfies a public health priority.

Reviews were prepared by Mrs Al-Fannah and Dr Hoppu. The Subcommittee also considered the proposal for treatment of respiratory tract infections in assessing these medicines. The 15th Model List includes 10 beta lactam

medicines on the Core List and three on the Complementary List. The following medicines are recommended and licensed for use in children and were endorsed by the Subcommittee as essential:

- amoxicillin
- ampicillin
- benzylpenicillin
- cloxacilllin
- phenoxymethylpenillin
- procaine benzylpenicillin.

In addition, the Subcommittee recommended that:

1. an additional strength of amoxicillin oral liquid (250 mg/5 ml) should be added to the list

2. it was noted that there were concerns about the use of procaine benzylpenicillin in neonates. However, this agent is extremely useful and is widely used in this age group, and a review of its use in neonates is requested.

The following medicines were originally flagged in the review of the list as having some uncertainty:

- amoxicillin + clavulanic acid
- benzathine benzylpenicillin
- cefazolin.

The Subcommittee considered the safety issue with amoxicillin-clavulanic acid (rare reports of cholestatic jaundice) and noted that as it is very uncommon in children it should not preclude endorsing this medicine as essential. Additional strengths were included: powder for suspensions 250 mg/62.5 mg per 5 ml and 125 mg/31.25 mg per 5 ml. Benzathine penicillin injection was included in recognition of its role in prevention in recurrent rheumatic fever and a lower dose vial 900 mg benzathine penicillin (=1.2 million IU) was added. Cefazolin was noted to be recommended for surgical prophylaxis in children in at least some countries and therefore was endorsed with a square box to indicate other first generation cefalosporins might be substituted as equivalent at a national level. The lack of an oral cephalosporin in the list was noted and the Subcommittee requested a review and preparation of a submission for the next meeting. The Subcommittee also noted the need for prescribing guidelines in countries to ensure appropriate use of antibiotics, given the increasing global problems caused by antimicrobial resistance.

The Subcommittee then considered the three medicines on the Complementary List, ceftazidime, ceftriaxone and imipenem + cilastatin. The commissioned review of respiratory tract infections identified ceftriaxone or cefotaxime as alternatives for severe pneumonia. The review of chloramphenicol (see below) also identified evidence that ceftriaxone is as effective as chloramphenicol in the treatment of meningitis and is the first-line treatment recommended for this in many countries. There are advantages in the dosing regimen for ceftriaxone as it can be given once daily. Ceftazidime is on the Complementary List intended only for the treatment of pseudomonas infections. A review of the appropriate treatment of pseudomonas infections is requested.

On balance, the Subcommittee decided to endorse ceftriaxone as essential on the Core List and list it with a square box indicating that other third generation cephalosporins might be selected at the national level. The Subcommittee endorsed a carbapenem as essential but maintained it on the Complementary List as it would require specialist facilities for use. Imipenem + cilastatin is currently listed but the Subcommittee identified that meropenem may be a preferred alternative for children. The Subcommittee requested a review of the carbapenems with an appropriate application submitted to the next meeting.

6.2.2 *Other antibacterials*

The current listing in the 15th EML includes: azithromycin, chloramphenicol, ☐ ciprofloxacin, doxycycline, ☐ erythromycin, ☐ gentamicin, ☐ metronidazole, nitrofurantoin, spectinomycin, sulfamethoxazole + trimethoprim, trimethoprim. ***Complementary List:*** *clindamycin, suldfadiazine, vancomycin*.

Reviews of this Section were provided by Mrs Al-Fannah and Dr Hoppu. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

As pneumonia is one of the major causes of morbidity and mortality, the Secretariat commissioned a review of antibiotics for the treatment of upper and lower respiratory tract infections. The Subcommittee considered the reviews for each of the antibiotics in the relevant Sections. In addition, the Subcommittee considered the following questions.

The clinical data summarized in the review suggest that there is no evidence for superiority of azithromycin versus erythromycin (or clarithromycin) or beta lactams. It would therefore seem appropriate to continue to restrict use to the currently specified indication of trachoma, noting that it is

not licensed for this purpose and the Cochrane review on this topic is inconclusive regarding the value of antibiotics.

There was concern about differences in both efficacy and safety between members of the macrolide group. The group endorsed the listing of erythromycin alone and requested a review of the macrolide group of drugs. The Subcommittee also noted that consideration should be given to the selection of erythromycin salt, as there may be differences in bioavailability of different preparations.

Ciprofloxacin is licensed for use in children in the UK and USA for specific indications, although the suspension formulation is not licensed in the UK for use in children under 2 years of age. The Subcommittee noted that there is much less experience of the use of other fluroquinolones (moxifloxacin, norfloxacin, ofloxacin) in children. As the Subcommittee accepted that ciprofloxacin is the drug of choice for the treatment of Shigella infection, it decided not to alter the current listing, but to remove the square box and the existing comment "final selection depends on indication for use". The Subcommittee expressed strong concern about the potential for the overuse and inappropriate use of fluoroquinolones outside this indication and requested a full review of the efficacy, safety and rational use of fluoroquinolones in children for the next meeting.

The Subcommittee noted that tetracyclines (including doxycycline) are contraindicated in children under 8 years of age because of their effects on the formation of bone and teeth discolouration. The Subcommittee noted that doxycycline was recommended for short-term use in children under 8 years of age for the treatment of cholera. In this context, the risk-benefit assessment was acceptable, and therefore the Subcommittee endorsed the listing of doxycycline with a note to indicate its use only for this purpose. The Subcommittee had no evidence to support the use of other tetracyclines for this purpose, so deleted the square box and requested a review of this question.

The Subcommittee endorsed the inclusion of gentamicin (with a square box listing) for inclusion on the EMLc. There were noted to be particular concerns in some countries about toxicity (especially ototoxicity) in children and the Subcommittee requested a review of the evidence on ototoxicity for the next meeting. The Subcommittee endorsed the inclusion of metronidazole on the EMLc but removed the square box listing.

The Subcommittee noted that nitrofurantoin is not recommended for use in neonates, or in children under three months of age. The Subcommittee endorsed the inclusion of nitrofurantoin on the EMLc. Given the need for

small doses in children aged 3 months to 12 years for the treatment and prophylaxis of urinary tract infections, the Subcommittee recommended the addition of an oral liquid 25mg/5ml formulation of nitrofurantoin to the EMLc.

Spectinomycin is used predominantly for the treatment of sexually transmitted diseases. The Subcommittee noted comments that other drugs are more efficacious and less toxic for the treatment of urinary tract infections in children. Therefore the Subcommittee decided to delete spectinomycin from the EMLc.

The Subcommittee considered and rejected a proposal that a note be added to the list recommending that co-trimoxazole be used only for *Pneumocystis Carinii* pneumonia prophylaxis in HIV-infected children.

Trimethoprim is used for urinary tract infections where there is evidence that bacteria are not resistant to it. The Subcommittee decided to retain trimethoprim in the EMLc and added a liquid dosage form, 50 mg/5 ml, to the list.

Complementary List

Clindamycin capsules and injection are licensed for use in children in the UK for the treatment of Staphylococcal bone and joint infections and peritonitis. The Subcommittee noted that clindamycin has been associated with antibiotic-associated colitis which may be fatal and that children should therefore discontinue treatment immediately if diarrhoea develops. The Subcommittee endorsed the inclusion of clindamycin capsules and injection on the EMLc and added a 75 mg/5 ml liquid formulation to the list.

The Subcommittee noted that sulfadiazine is contraindicated in preterm infants and in neonates < 4 weeks old (except for congenital toxoplasmosis) due to an increased risk of kernicterus. Sulfadiazine is used in combination with pyrimethamine for the treatment of toxoplasmosis, however sulfadiazine is not licensed for use in children for this indication. The Subcommittee decided to retain the listing of sulfadiazine on the EMLc and review this at the next meeting. The Subcommittee noted the need for the development of a paediatric formulation of sulfadiazine.

Vancomycin is used intravenously for the prophylaxis and treatment of endocarditis and other serious infections caused by Gram-positive cocci. The Subcommittee noted the increased risk of nephrotoxicity in children due to immature renal function (especially in preterm infants), the need for therapeutic drug monitoring and the importance of slow infusion of

vancomycin. The Subcommittee endorsed the inclusion of vancomycin on the EMLc.

Chloramphenicol

Chloramphenicol has been included on the Model List of Essential Medicines since the first list was developed in 1977. At the time, it was noted that the benefits of using chloramphenicol outweighed the risks, although the adverse events were known and potentially severe. Currently in the WHO *Pocket Book of Hospital Care for Children* it is recommended for:

1. treatment of meningitis in young infants (powder for injection)
2. an alternative for treatment of severe pneumonia (IV powder for injection)
3. treatment of empyema
4. as an alternative when erythromycin is not available for the treatment of pertussis (oral)
5. as treatment for meningitis during an epidemic (IM injection, or IV), with ampicillin
6. as treatment for sepsis (with benzylpenicillin)
7. as treatment of typhoid
8. as treatment of mastoiditis
9. as treatment of osteomyelitis or septic arthritis in children < 3 years.

WHO has also recommended the use of oily chloramphenicol injection as treatment for presumptive treatment of epidemic meningitis in peripheral health centres since 1996.

Over the past year, letters have been sent by individuals to WHO requesting that chloramphenicol be removed from the Model List of Essential Medicines because of its adverse effects. This was also discussed briefly at the Expert Committee meeting in 2005, in the context of the review of ceftriaxone 1 g injection. The Secretariat therefore commissioned a review of the current evidence of effectiveness and safety of the medicine.

Comments were received from the WHO Department of Epidemic and Pandemic Alert and Response, recommending retaining oily chloramphenicol on the list for use in epidemic meningitis and this was also supported by the Ministries of Health of Togo and Sudan, and also MSF.

The Subcommittee considered the review and noted that the review examined the evidence for retaining chloramphenicol as first-line therapy on the Model List for the treatment of bacterial meningitis and for the use of oily chloramphenicol injection in meningococcal meningitis epidemics.

The available randomized controlled trial evidence suggests that third generation cephalosporins are as effective as standard treatment regimens that include chloramphenicol for the treatment of bacterial meningitis. Once or twice daily dosing schedules with ceftriaxone are more convenient than the four times daily schedules required for chloramphenicol and ampicillin regimens. There is also some evidence to suggest that shorter courses of treatment may be possible with ceftriaxone. Many of the trials were conducted in the 1980s and 1990s. It is difficult to apply the results of these studies to current routine practice, where the effectiveness of chloramphenicol may be markedly reduced with increasing evidence on the emergence of chloramphenicol-resistant strains of *Haemophilus influenzae*. Over time, the prices of third generation cephalosporins have also come down, so the price differentials are smaller. In some settings, treatment with ceftriaxone may be cheaper than with chloramphenicol.

Adverse effects of chloramphenicol, specifically grey baby syndrome when it is used in neonates, were considered. There were no reports of the severe haematological side-effects that have led to limited use of chloramphenicol in developed country settings. In the trials available, ceftriaxone was often associated with more adverse effects than conventional therapy, particularly more diarrhoea. The side-effects of chloramphenicol remain a concern, but the balance of benefits versus harms favours use of chloramphenicol in severe life-threatening infections.

Ceftriaxone has also been shown to be as effective as oily chloramphenicol injection for meningococcal meningitis epidemics. However, the Subcommittee noted the problems of prepositioning ceftriaxone because of diversion.

It was recognized that superior antibiotics are widely available for many of the indications for which chloramphenicol was used. Chloramphenicol oily injection was considered essential for epidemic meningitis to be used as per the WHO protocol (standardized treatment of bacterial meningitis in Africa in epidemic and non-epidemic situations, WHO 2007). Chloramphenicol also had a role in the treatment of enteric fever, severe pneumonia and in rickettsial disease. The risk of using chloramphenicol in neonates (grey baby syndrome) was recognized and it was felt that this should be identified in dosing and treatment guidelines.

The Subcommittee considered both the risks and benefits of chloramphenicol and decided to retain all currently listed forms of chloramphenicol on the Model List for use in meningococcal meningitis epidemics and severe life-threatening infections.

6.2.3 *Antileprosy medicines*

Section 6.2.3, antileprosy medicines, includes: clofazamine, dapsone and rifampicin as capsules or tablets.

All three can be supplied as co-packed blister packs through WHO and are licensed for the treatment of leprosy. A review of this Section was prepared by Dr Jeena and by Dr Peterson.

The Subcommittee endorsed these three medicines as essential. The question of whether an oral liquid form of rifampicin should be added to the List was discussed, but as the three medicines are supplied in combination packs as part of standard treatment programmes, it was considered inappropriate. An appropriate paediatric dose form is needed.

6.2.4 *Antituberculosis medicines*

In March 2007, some of the medicines on the Model List for the treatment of tuberculosis were revised.

The current listing in the 15th EML includes ethambutol tablets, isoniazid, tablets (scored), pyrazinamide (dispersible and scored tablets), rifampicin tablets and streptomycin injection, plus several fixed-dose combinations for treatment of non-resistant TB, plus on the ***Complementary List:*** amikacin, p-aminosalicylic acid, capreomycin, cycloserine, ethionamide, kanamycin and ofloxacin for resistant TB.

Reviews of this Section were prepared by Dr Jeena and Dr Peterson.

There are no international data publicly available that describe the prevalence and incidence of TB in children under 15 years of age, and few clinical trials of treatment on children. However, TB is accepted as a public health priority and therefore treatment of it fulfils the criteria for essential medicines. All four medicines used in standard treatment are licensed for use in children. The Subcommittee endorsed all four and noted that an oral liquid form of all of them was available. The Subcommittee recommended that all of these single agents be added to the List (ethambutol 25 mg/ml, isoniazid 50 mg/5 ml, pyrazinamide 30 mg/ml, rifampicin 20 mg/ml).

The role for streptomycin was clarified as being required in the treatment of TB meningitis and reactivated TB. It is recommended in the WHO treatment guidelines for use in children. The Subcommittee discussed the role of substituting other aminoglycosides and the Subcommittee therefore requested that this class of medicines should be reviewed but decided to endorse the current listing of streptomycin at this meeting.

The various fixed-dose combinations were considered as a group, as there is no clinical evidence for any of these combinations in children. However, it is difficult to determine the necessary appropriate combinations and what the strengths of the components should be in FDCs for use in children without examining further data (including pharmacokinetic data, stratified by weight and age). The Subcommittee therefore decided to endorse the lower strength rifampicin + isoniazid combinations (60 mg + 30 mg and 60 mg + 60 mg) and rifampicin + isoniazid + pyrazinamide (60 mg + 30 mg + 150 mg) as probably useful for many children, but requested an urgent review of all clinical evidence to support these and other potential combinations.

The Subcommittee then reviewed the medicines currently listed for the treatment of MDR-TB. There is limited, if any, clinical evidence for use of these medicines in children for this indication although some of them are licensed for other indications. The Subcommittee recognized the need for including medicines for this purpose and added a note to the list indicating that the use of these drugs in children was to be reviewed for the next meeting. Recognizing the public health importance of this condition, the Subcommittee requested that the Secretariat should give the reviews of medicines for TB in children, including first- and second-line treatment, the highest priority.

Section 6.3 Antifungal medicines

The current listing in the 15th EML includes: clotrimazole, □ fluconazole, griseofulvin, nystatin. ***Complementary List:*** amphotericin B, flucytosine, potassium iodide.

Reviews of this Section were prepared by Professor Cranswick and Dr Dai. There were two new applications for additions to this Section (caspofungin and terbinafine). No additional comments were received.

The Subcommittee noted that vaginal preparations of clotrimazole were not needed in the EMLc and therefore deleted clotrimazole from this Section. Nystatin pessaries were also deleted from the EMLc.

The Subcommittee endorsed listing of fluconazole (capsule, injection and oral liquid formulations currently listed on the 15th EML) on the EMLc but without a square box listing.

The Subcommittee endorsed the listing of griseofulvin on the EMLc in the dose forms currently listed on the 15th EML. Nystatin was endorsed as an essential medicine for children and included in the EMLc (lozenge and tablet

formulations). Recognizing the need for oral nystatin for intestinal and oral candidiasis in young children, the Subcommittee recommended the addition of a nystatin liquid formulation on the EMLc (100 000 IU/ml, 30 ml).

The Subcommittee endorsed the listing of amphotericin B, flucytosine (capsule and infusion formulations) and potassium iodide saturated solution on the EMLc. The Subcommittee also noted the need for affordable liposomal amphotericin B products. The Subcommittee noted the difficulty in sourcing flucytosine infusion and felt that this should be more available.

The Subcommittee considered two new applications for the addition of caspofungin (Complementary List) and terbinafine to Section 6.3.

Caspofungin is FDA approved for invasive aspergillosis for patients intolerant to first-line drugs (amphotericin B) or not responding to therapy, for oesophageal candidiasis, for deep and invasive candidiasis and empirical therapy for fever in neutropenic patients. It is administered by IV infusion over 1 hour. The clinical data suggest caspofungin is effective and comparable to amphotericin B and fluconazole for the treatment of oesophageal candida infections and comparable to amphotericin B for treatment of candidemia in adults. However there are limited data available on the safety and efficacy of caspofungin in children. The Subcommittee also noted comments in the British National Formulary for Children (BNFC) that caspofungin is not licensed for use in children. The Subcommittee decided that at present there are insufficient clinical data on the efficacy and safety of caspofungin in children to be able to list this medicine on the EMLc and therefore rejected the application.

Terbinafine is used orally for treating onchomycosis and other dermatophyte infections requiring systemic therapy. Clinical data provided suggest that terbinafine (2-4 weeks) is similar to griseofulvin (6-8 weeks) for treating Trichophyton infections; it has been shown superior to griseofulvin, itraconazole and ketaconazole for the treatment of onichomycoses, and safe and effective in children for this indication. Terbinafine has been shown superior to griseofulvin for fungal skin infections of the foot, and equally effective for treatment of tinea imbricata. Terbinafine is well tolerated orally. Adverse effects include GI effects, headache, rash and rarely Stevens-Johnson syndrome. Rare hepatotoxicity has been reported. The application noted that terbinafine therapy is more expensive than griseofulvin, however, terbinafine is clinically superior and may be associated with better rates of compliance.

The Subcommittee noted BNFC comments comments that terbinafine is not licensed for use in children in the UK and considered that at present

there are insufficient clinical data on the efficacy and safety of terbinafine in children to be able to list this medicine on the EMLc. The Subcommittee therefore rejected the application for listing of terbinafine.

Section 6.4 Antiviral medicines

The current listing in the 15th EML includes:

6.4.1 Antiherpes medicines: ☐ aciclovir.

6.4.2 Antiretrovirals:

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors: abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), tenofovir disoproxil fumarate (TDF), zidovudine (ZDV or AZT).

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors: efavirenz (EFV or EFZ), nevirapine (NVP).

6.4.2.3 Protease inhibors: indinavir (IDV), lopinavir + ritonavir (LPV/r), nelfinavir (NFV), ritonavir, saquinavir (SQV).

Fixed-dose combinations: efavirenz + emtricitabine + tenofovir, emtricitabine + tenofovir, stavudine + lamivudine + nevirapine, zidovudine + lamivudine, zidovudine + lamivudine + nevirapine.

6.4.3 Other antivirals: ribavirin.

6.4.1 *Antiherpes medicines*

The Subcommittee considered two medicines listed as antivirals: aciclovir, listed in Section 6.4.1 as an antiherpes medicine and ribavirin, listed in Section 6.4.3 and added in March 2007 for the treatment of viral haemorrhagic fevers. Review of ribavirin was prepared by Professor Cranswick.

Aciclovir was noted to be licensed as the injection for use in children, for varicella-zoster infection and herpes simplex infection. The Subcommittee endorsed the inclusion of the injection and tablet forms of acyclovir on the EMLc and added the oral liquid form (200 mg/5 ml) to the list.

6.4.2 *Antiretrovirals*

Section 6.4.2 of the WHO Model List of Essential Medicines includes antiretrovirals, the majority of which were added to the List in 2002. The Section on fixed-dose combination products was added in March 2007.

The Subcommittee considered a number of individual applications for modifications to the current listing and new fixed-dose combination products (see below). Of those products currently on the list, the Subcommittee noted that for Section 6.4.2.1, nucleoside/nucleotide reverse transcriptase inhibitors, didanosine, lamivudine and stavudine are all approved for use in children and have a well-established place in the treatment of HIV. All dosage forms listed were endorsed, except the 40 mg stavudine capsule.

The didanosine buffered powder for oral liquid already included on the Model List was recognized as having problems with dosing but was retained on the list as it may be the only product currently available in some settings. The Subcommittee requested that alternative child-friendly products be made available. The stavudine oral liquid was recognized as being problematic as the volume required for oral dosing was too high and requires refrigeration. An alternative, more appropriate formulation is required.

Emtricitabine was noted to have been added to the EML in March 2007 and was licensed for use in children > 3 months of age. Tenofovir, also a new addition to the list, is not approved for use in children under 18 and therefore was not endorsed for the EMLc.

For Section 6.4.2.2, nevirapine was endorsed as essential. It was noted that the single dose sachets were desirable for the prevention of mother to child transmission programmes and should be added to the EMLc when they become available. Efavirenz is not licensed for use in children less than 3 years of age or weighing under 10 kg, and therefore was endorsed as essential but with a note specifying the age and weight restriction.

The protease inhibitors included in Section 6.4.2.3 were reviewed by the Subcommittee. Lopinavir + ritonavir, nelfinavir and saquinavir were endorsed as essential in the forms listed, although the need for a heat-stable combination of lopinavir + ritonavir was also considered. Saquinavir was annotated with a note that it was to be used in children > 25 kg. The ritonavir liquid formulation was recognized as extremely problematic because of the taste and the inclusion of alcohol as a major excipient.

The Subcommittee noted that indinavir was not licensed for use in children and was therefore not endorsed. The Subcommittee noted that this Section was marked for review at the next Expert Committee meeting and suggested that it should also be reviewed with respect to identifying priority protease inhibitors for use in children.

New application: Abacavir (scored tablet 300 mg): Section 6.4.2.1

Medicines for treating HIV have been on the main Model List of Essential Medicines since 2002, including several dosage forms of different products for children. Abacavir has been listed as a 300 mg tablet as well as an oral liquid formulation. In this application, lodged by GlaxoSmithKline, the requested listing is for a 300 mg *scored* tablet.

Reviews of the application were prepared by Dr Zaidi. The application relied on the previous submission to the Expert Committee in 2002 and did not provide any additional clinical information. A limited search of literature undertaken by the Secretariat identified several potentially relevant citations. Of these, there were six relevant studies: two clinical trials, three pharmacokinetic studies and one population pharmacokinetic study. The results of the clinical trials *(1, 2)* established the effectiveness and safety of abacavir in children and the remaining studies *(3-6)* support the current dosage regimen (8 mg/kg twice daily). All were using the current standard formulation of abacavir rather than the proposed dosage form.

Given that the approved dose for children is 8 mg/kg twice daily, a half tablet (150 mg) would potentially allow children down to 10 kg to use the tablet rather than liquid dosage form. WHO guidelines recommend that the tablet can be crushed and given immediately with food or liquid; this is based on clinical experience rather than clinical trials. The US approved Product Information notes that the absorption of the tablet is not altered by food.

The Subcommittee noted that the new form has been submitted to the EMEA for approval but is not yet approved. The application states that, once approved, the scored form of tablet will replace the unscored form globally, including not-for-profit supply. The Subcommittee noted that the scored 300 mg tablets are covered by the tablet listing and would be appropriate to include on the EMLc once licensing approval has been granted, given that there is clinical trial and pharmacokinetic evidence to support the use of abacavir in children.

New application: Lamivudine (scored tablet 150 mg)

Lamivudine has been listed on the WHO Model List since 2002 as a 150 mg tablet as well as an oral liquid formulation. In this application, lodged by GlaxoSmithKline, the proposed list is for a 150 mg *scored* tablet for use in children down to 12 kg.

Reviews of the application were prepared by Dr Zaidi. The application relied on the previous submission to the Expert Committee in 2002 and did not

provide any additional clinical information. The Secretariat identified several relevant studies *(1-3, 7-16)*. The results of the clinical trials established the effectiveness and safety of lamivudine in children. Doses used in the clinical trials range from 4-8 mg/kg by using either the current standard solid dose formulation or oral liquid rather than the proposed dosage form.

Given that the apparent wide dose range of lamivudine does not appear to be associated with increased toxicity, a half tablet (75 mg) would potentially allow children down to 12 kg to use the tablet rather than liquid dosage form. The Subcommittee noted that the new form has been submitted to the EMEA for approval but is not yet approved. The Subcommittee noted that the scored 150 mg tablets could be included in the tablet listing and would be appropriate to include on the EMLc once licensing approval has been granted.

Fixed-dose combinations

Lamivudine + zidovudine

In March 2007, several FDC products for HIV were added to the Model List in combinations appropriate for use in adults. The Subcommittee considered an application from GlaxoSmithKline (GSK) for a new dosage form: a scored tablet containing lamivudine + zidovudine: 150 mg+300 mg. A review of the application was prepared by the Secretariat.

The key role of FDC products in scale-up of HIV treatment programmes has been established and the WHO Department of HIV has been working with a group of experts over the past 18 months to establish recommended doses of components of FDC products for children, to allow simplified dosing schedules (twice daily) with a standardized product across all age ranges. Half tablets of this particular combination could be used for children from 14 kg up, in combination with nevirapine for example.

The application relies on the application presented for the Expert Committee in March 2007 (see: http://mednet3.who.int/EML/expcom/expcom15/applications/formulations/AZT3TCapplication.pdf). An additional review of the published literature on combination treatment in children was undertaken by the Secretariat which identified six studies as potentially relevant *(1, 10, 11, 16-18)*. These studies are in addition to those identified in the application, which were trials conducted mainly in adults. All of the studies used doses that are within the recommended dose range for the components.

The safety of these products in combination has been clearly defined. Although there are well recognized toxicities with both components, dosing regimens and treatment schedules can be adjusted to manage these.

The application does not provide cost data but notes that the scored form of tablet will replace the unscored form globally once it is registered.

The Subcommittee considered that FDC products for HIV are clearly essential. There is sufficient clinical evidence of effectiveness and safety of these medicines used in loose combination and as fractions of adult FDCs. The Subcommittee noted that the new form has been submitted to the EMEA for approval but is not yet approved. As this product is a scored variant of a FDC that is already listed, the Subcommittee endorsed its inclusion in the EMLc once licensing approval was granted, noting that appropriate quality of any FDC would need to be ensured at national or programme level.

New application: Triple fixed-dose combinations

The Subcommittee then considered two applications for triple FDCs, from Ranbaxy: lamivudine + stavudine + nevirapine, in two strengths: 40 mg + 10 mg + 70 mg OR 20 mg + 5 mg + 35 mg, and Lamivudine + zidovudine + nevirapine: 30 mg + 60 mg + 60 mg.

A review of these applications was provided by Dr Kazembe. The comments from the WHO HIV Department on the proposed ideal components and characteristics of FDCs for children were also noted.

With regard to the first combination, the application presents a review of the published literature of combination treatment and the results of one bioequivalence study with the proposed combination. There are no clinical trials in children with the proposed FDC and therefore clinical efficacy has to be inferred from studies of the components given individually or in loose combination. The Secretariat's literature search identified seven additional studies as potentially relevant *(9, 12, 19-23)*. Most of these used adult FDC products, dosed in fractions for different weight bands of children. All of the studies used doses that are within the recommended dose range for the components, and this triple FDC would have a similar dosing schedule except in very small children.

The safety of these three products in combination has been clearly defined. Although there are well recognized toxicities with all three components, dosing regimens and treatment schedules can be adjusted to manage these. Stavudine may have advantages in the initial treatment of small children as it is easier to use in the presence of anaemia than zidovudine, but it should not be used in children under 5 kg using either FDC proposed here.

The Subcommittee noted that the cost per year of using the low-strength FDC is stated in the application to be US$ 64.80. A comparison with the single components is provided based on the 2006 prices, and the FDC is

substantially cheaper. The Subcommittee considered that there is sufficient clinical evidence of effectiveness and safety of these medicines used in loose combination and as fractions of adult fixed-dose combinations. These particular combinations could be used in children, although not in children under 5 kg, because of the risk of stavudine excess. On balance, due to the uncertainty about the precise dose of the components that would be desirable, these proposed FDCs were not added to the list. The Subcommittee discussed the challenges of dosing in children and the problems of doses based on body surface area (BSA) and weight bands. The Subcommittee recognized that BSA was rarely estimated in clinical practice, and that doses based on weight were more appropriate. The attempts to combine dose recommendations based on BSA and converting those to doses appropriate to weight contributed to the difficulties in establishing appropriate FDCs suitable for use in children of a variety of weight bands.

The second combination (lamivudine + zidovudine + nevirapine: 30 mg + 60 mg + 60 mg) was noted to be still in development. There are as yet no clinical trials in children with the proposed FDC and therefore clinical efficacy has to be inferred from studies of the components given individually or in loose combination. The Secretariat's literature search identified six studies as potentially relevant as having used either the three components or two out of three components in the proposed triple FDC in children. These studies are in addition to those identified in the application, which were mainly in adults. All of the studies used doses that are within the recommended dose range for the components, and this triple FDC would potentially have a similar dosing schedule.

While welcoming the proposed development, the Subcommittee noted that as this product is still not yet available, it is premature to include on the EMLc.

6.4.3 *Other antivirals*

Ribavirin was added to the list in March 2007 for use for viral haemorrhagic fevers, including use in children. The Subcommittee recommended that this be included on the list as essential for children but, given concerns about potential inappropriate use of this medicine in children, added a note that it was for the treatment of viral haemorrhagic fevers only.

Section 6.5 Antiprotozoal medicines

Infections due to protozoa are common in children especially in developing countries and therefore medicines to treat these infections are essential medicines for children.

The current listing in the 15th EML includes:

6.5.1 Antiamoebic and antigiardiasis medicines: diloxanide, ☐ metronidazole.

6.5.2 Antileishmaniasis medicines: ☐ meglumine antimonite, paromomycin. ***Complementary List:*** *amphotericin B, pentamidine*.

6.5.1 *Antiamoebic and antigiardiasis medicines*

There were no applications for additional medicines for this Section and no additional comments were received.

The Subcommittee noted that diloxanide was not licensed in the UK for use in children < 25 kg body weight. Diloxanide was medicine of choice for asymptomatic patients with *E. histolytica* cysts in the faeces and has a role as adjunctive medicine against hepatic amoebiasis, given after a course of metronidazole or tinidazole.

Metronidazole is not licensed for use in neonates or children under 1 year while tinidazole is licensed for intestinal amoebiasis in children (age not specified).

The Subcommittee therefore recommended that metronidazole (and tinidazole which would be covered by square box listing of metronidazole) be endorsed as essential medicines in the forms currently available in the 15th EML.

The Subcommittee endorsed the inclusion of diloxanide in the EMLc, with a note to indicate it should be used in children > 25kg. The Subcommittee requested a review of diloxanide for the next meeting, with efficacy and safety data compared to oral paromomycin for amoebiasis.

6.5.2 *Antileishmaniasis medicines*

A review of this Section was prepared by Dr Sachdev. No applications for additional medicines for this Section were submitted.

The Subcommittee noted that pentavalent antimony (meglumine antimoniate and sodium stibogluconate) is recommended for treating leishmaniasis. Sodium stibogluconate is licensed for use in children and there is much more experience with its use in children than for meglumine antimoniate.

Paromomycin was considered at the 15th Expert Committee meeting in March 2007, where paromomycin solution for intramuscular (IM) injection was added to the Model List, see: http://www.who.int/medicines/services/

expertcommittees/essentialmedicines/15_MAY_TRSreport.pdf). The Expert Committee concluded that paramomycin was effective in terms of effect on standard endpoints, such as initial and final cure, for the treatment of visceral leishmaniasis in children and adults. Paromomycin is licensed in India, and has been granted orphan drug designation by the US Food and Drug Administration (FDA) in March 2005 and the European Medicines Agency (EMEA) in April 2005.

The Subcommittee noted that amphotericin B has been used in cases resistant to sodium stibogluconate with good results as well as for systemic fungal infections.

Pentamidine isetionate has been relatively rarely used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high and it is associated with serious side-effects.

The Subcommittee therefore recommended that because of the licensing and greater experience with use of sodium stibogluconate, it should be first listed pentavalent antimony agent for use in children. The Subcommittee recommended that meglumine antimoniate would also be identified in the EMLc and the square box removed. The Subcommittee endorsed the listing of paromomycin, amphotericin B and pentamidine on the EMLc.

6.5.3 *Antimalarial medicines*

6.5.3.1 For curative treatment

The current listing in the 15th EML includes: amodiaquine, artemether, artemether + lumefantrine, artesunate, chloroquine, doxycycline, mefloquine, primaquine, quinine, sulfadoxine + pyrimethamine.

Section 6.5.3.1 was completely updated at the March 2007 meeting of the Expert Committee. The Subcommittee considered a number of new applications for antimalarial products (see below).

For those products already on the list, the Subcommittee endorsed amodiaquine, artemether, artemether + lumefantrine, artesunate, mefloquine, primaquine, quinine, sulfadoxine + pyrimethamine as essential, including the comments regarding use in combination.

The Subcommittee considered whether chloroquine syrup is essential. It noted that use was very restricted and also noted comments from MSF regarding problems with the formulation of the liquid, leading to a serious risk of toxicity. However, the need for chloroquine to treat sensitive *P.vivax* malaria was recognized and so recommended that the syrup should be endorsed.

Doxycycline was considered as appropriate to include only for use in combination with quinine (even though it is usually contraindicated in children under 8 years). The Subcommittee noted that an alternative recommended regimen for severe malaria is quinine plus clindamycin and suggested that these medicines should be considered for inclusion as an antimalarial at its next meeting.

6.5.3.2 For prophylaxis

The current listing in the 15th EML includes: chloroquine, doxycycline, mefloquine, proguanil.

For Section 6.5.3.2, the Subcommittee first considered whether there was a need for inclusion of essential medicines for prophylaxis of malaria for travellers on the EMLc. Having decided that there was a need, the Subcommittee endorsed chloroquine to be used with proguanil.

The Subcommittee endorsed doxycycline for inclusion in the EMLc but with a note indicating an age limit (> 8 years). Mefloquine was endorsed by the Subcommittee with a note to be used in children aged > 3 months or > 5 kg. The Subcommittee requested that a liquid form of proguanil becomes available. The Subcommittee endorsed the inclusion of proguanil on the EMLc.

New application: Artemether injection

Artemether injection (80 mg/ml oily injection) was added to the WHO Model List in 1997. After a review of the malaria Section on the list in March 2007, it was moved from the Complementary List to the Core List, in line with the WHO Guidelines for Treatment of Malaria (2006). Dafra Pharma has submitted a new application for a new dosage form and strength for artemether–20 mg/ml injection, with miglyol as solvent.

A review was prepared by Dr Jeena and comments were received from MSF.

The application presents a narrative summary of the results of approximately 40 studies of the use of artemether in the treatment of malaria. Of these, 15 were studies in children. The search strategy for identifying these studies was not described and two systematic reviews are not included. A recent review *(24)* is more rigorous and identifies a further three studies comparing intramuscular injection of artemether with injectable quinine in children with severe malaria *(25-27)*. In these trials, there were generally no differences between treatment groups for mortality,

parasite clearance time and fever clearance time. Adverse effects seem to be fewer with artemether injection than with intravenous quinine.

Taking all of the evidence together, artemether intramuscular injection is probably as effective as intravenous quinine. The dosage regimen used is 3.2 mg/kg as a loading dose followed by 1.6 mg/kg/day for an additional 4 days. Theoretically, a 20 mg/ml ampoule might be useful for children up to 6 kg for the loading dose and for children up to 10-12 kg for the follow-up doses as a single ampoule injection.

The major uncertainty is the pharmacokinetics of this product, which uses coconut oil as a solvent, although the Subcommittee noted this was the same vehicle used in the 80 mg/ml product made by this manufacturer. The WHO Guidelines for Treatment of Malaria (2006) note that absorption of artemether following intramuscular injection is very variable, particularly in patients with severe malaria who may have circulatory impairment. There is one study of the kinetics of artemether in miglyol in adults described in the application. This is a non-comparative study, unpublished, carried out by Dafra Pharma and the description of the study in the application is not adequate to allow any assessment of the validity of the results.

The application provides a comparison of some prices for artemether products and quinine. The proposed price for this product is US$ 3.62 for 10 ampoules of 20 mg/ml.

The Subcommittee considered that the lower strength injection may be of value in small children with severe malaria. The solvent of the submitted product is possibly acceptable according to current pharmacopoeial monographs. The Subcommittee noted that the application reported that the product was being considered by the EMEA and therefore recommended that the additional strength of injection be added to the Model List, once approved by the regulatory authority.

New application: Artemether + lumefantrine fixed-dose combination

Artemether + lumefantrine is a recommended FDC for the treatment of malaria and has been listed as a tablet containing 20 mg artemether + 120 mg lumefantrine on the EML since 2002. An application submitted by Dafra Pharma, for a paediatric suspension powder for oral suspension, 120 ml containing 360 mg β-artemether plus 2160 mg lumefantrine, was considered at the March 2007 meeting of the Expert Committee and rejected, on the grounds of inadequate evidence of efficacy of the proposed dosage regimen. The application has been resubmitted.

Reviews of the application were prepared by Dr Jeena. Additional comments were received from the WHO Global Malaria Programme.

The application re-presents the same three clinical trials considered in March, plus the results of a bioequivalence study. The summary argument made in the covering letter is that:

— "*The dosage regimen proposed is not limitative and the standard dose based on single administration per day of 4mg/kg (with 6 fold the lumefantrine dose) is a safe and adequate dosage regiment* [sic] *for children.*
— *The product proposed is perfectly bioequivalent with Coartem tablets.*
— *The evidence we provide with our clinical trials comes on top of existing evidence available in the literature where it is stated that the artemether/lumefantrine FDC combination is efficacious and safe. Evidence on safety and efficacy of the dosages and regimen is provided in this submission."*

As noted above, the same data from three clinical trials are presented to establish the efficacy and safety of the new formulation in children. However, the Committee noted that none of the trials are rigorous randomized controlled trials comparing the combination suspension with either the combination tablet preparation, or the two drugs administered concomitantly, in the same population. There are no dose-ranging studies to establish that the dosage regimen as proposed in the application is effective across all weight bands of children. The table below compares the dose as recommended by the WHO treatment guidelines with the dose proposed for the suspension.

Treatment doses for children of artemether by formulation

Weight of child	Artemether doses			
	Dose per day	Dose per course	mg/kg per day	mg/kg per course
Tablet formulation* (20 mg artemether, 120 mg lumefantrine)				
5 kg	3 tabs = 60 mg	6 tabs = 120 mg	12 mg/kg	24 mg/kg
10 kg	3 tabs = 60 mg	6 tabs = 120 mg	6 mg/kg	12 mg/kg
14 kg	3 tabs = 60 mg	6 tabs = 120 mg	4.3 mg/kg	8.6 mg/kg
Suspension formulation (3 mg artemether, 18 mg lumefantrine per ml)				
5 kg	7 mls = 21 mg	21 mls = 63 mg	4.2 mg/kg	12.6 mg/kg
7.5 kg	10 mls = 30 mg	30 mls = 90 mg	4.0 mg/kg	12.0 mg/kg
10 kg	14 mls = 42 mg	42 ml = 126 mg	4.2 mg/kg	12.6 mg/kg
15 kg	20 mls = 60 mg	60 mls =180 mg	4.0 mg/kg	12.9 mg/kg

* WHO Guidelines for the treatment of malaria. Geneva, World Health Organization, 2006.

The recommended dosing schedules mean that the suspension formulation provides a lower mg/kg dose per day and mg/kg dose per course for children weighing 5-10 kg, the likely target for this preparation. The dosing schedules result in similar mg/kg per day doses for children weighing 14-15 kg but higher treatment course doses for these children with the suspension rather than tablet formulation (12.9 mg/kg versus 8.6 mg/kg per course).

The Committee noted that the application describes the safety profile of artemether-lumefantrine based on patient experience with the combination tablet formulation (mild side-effects including trouble sleeping, nausea, vomiting, abdominal pain, dizziness and pruritus). Based on the limited experience of the three trials of the suspension formulation, only 3 of 259 children reported mild and spontaneously resolving side-effects (nausea, diarrhoea).

The bioequivalence study carried out in 42 healthy adults compared the bioavailability of Coartem tablets with the suspension. This is an unpublished study conducted in 2007 and the information provided in the application does not allow independent assessment of the validity of the results, which are claimed to show that the two products are bioequivalent.

The Subcommittee noted that the application suggests that the current FDC (20 mg + 120 mg) is *overdosing* lower weight children and also may be *underdosing* higher weight children. The application also proposes that the dose can be adjusted according to severity of the illness, but does not provide detailed instructions for doing so. No clinical evidence is provided to support these claims. Furthermore, this particular FDC was not supported by equivalent studies with the loose combination. The WHO Global Malaria Programme notes the problem with administering accurate doses of the suspension even at the proposed dosage regimen as the reconstitution volumes were difficult in a developing world setting in the absence of dosing syringes. The Subcommittee therefore concluded that there is still insufficient clinical evidence to support adding this FDC to the WHO Model List of Essential Medicines for Children and rejected the application. The Subcommittee also suggested that further applications for this product should not be considered without additional high-quality clinical trials of sufficient size (i.e. sample size calculated with an appropriate statistical analysis plan to demonstrate equivalence of the proposed combination at the proposed dose with current therapy), or other data as suggested in the WHO Technical Report Series No. 929 (Annex 5, Fixed-dose combinations).

New application: Artesunate (rectal capsules)

At the March 2007 meeting, the Expert Committee considered an application from the Global Malaria Programme (GMP), WHO, for the addition of

rectal artesunate as well as artesunate injection. The report of the meeting states:

> *"The Committee noted the potential value of rectal dosage formulations and overall the evidence provided in the application supports the public health need, effectiveness and safety of artesunate formulations for emergency use in adults and children for treating severe malaria. However, the Committee noted that the regulatory status of the products, particularly the rectal capsule, was unclear. The Committee therefore recommended that artesunate ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution be added to the core list of the 15th WHO Model List with the note: "for use in the management of severe malaria". The Committee decided, given uncertainty about current rectal products, to refer review of the rectal form to the paediatric Subcommittee meeting and recommended further research on rectal dosage forms."*

No new information on the regulatory status of the rectal artesunate products was provided. The Mepha product could not be found on either EMEA or FDA databases but does appear to be registered in a number of African countries.

Reviews of the application were prepared by Dr Deen and Dr Macleod. Additional comments were received from the WHO Global Malaria Programme.

Since the application was originally submitted, a systematic review of rectal administration of artemisinin derivatives has been published *(28)*. The authors of the review identified 20 published studies of rectal artesunate 50 mg and 200 mg suppositories, and three unpublished studies, plus a further two unpublished studies using the Scanpharm product. Of these, 18 published studies and five unpublished studies were included in the review, in both severe and uncomplicated malaria. Ten of the identified studies included children (n=481 total). Doses used were stratified into < 5 mg/kg and > 5 mg/kg.

The Committee considered the results of the studies, including the pharmacokinetic studies, as summarized in Tables 2 and 3 in the review. Results from studies using the lower doses suggest slower parasite clearance times than the higher dose studies. A total of 8 deaths were reported (all patients) in the studies of severe or moderately severe malaria, although the classifications of 'severe' disease were not consistent across studies. The review did not identify any comparative studies in addition to the studies presented in the GMP application.

The results of the pharmacokinetic studies showed marked inter-individual variability in pharmacokinetic parameters. The review notes that bioavailability of artesunate has been reported to be as low as 6%, but also notes that even very low plasma concentrations are likely to inhibit parasites. The impact of this on potential development of resistance is not discussed.

No information about cost or cost-effectiveness of the rectal preparations was provided.

Overall, the Subcommittee considered that there is clinical evidence that supports the effectiveness of rectal artesunate suppositories as pre-referral treatment of severe malaria at doses of 10 mg/kg, although the Subcommittee recognized that the interpretation of these data is hampered by the relatively poor quality of the trials. As noted in the published systematic review, these products have not been adequately developed and although they are available and in use, none has yet been approved by a stringent regulatory authority or the WHO Prequalification Programme. No cost information is provided. However, given the clinical evidence of benefit and safety of rectal artesunate in the pre-hospital treatment of malaria and the absence of alternative treatments in affected children, it was recognized that the addition of these rectal capsules to the Model List at the current time may provide an incentive for necessary further development of these products. The Subcommittee recommended that artesunate rectal capsules, 50 mg and 200 mg, be added to the Model List. The listing should include a note that the preparation is only to be used as a single dose for pre-referral treatment and that children must be taken to an appropriate health facility for follow-up care.

New application: Artesunate + amodiaquine fixed-dose combination

Sanofi-Aventis submitted an application for inclusion of a FDC containing 25 mg/67.5 mg, 50 mg/135 mg, 100 mg/270 mg artesunate and amodiaquine respectively. Currently amodiaquine 153 mg and 200 mg (as hydrochloride) tablets are listed for use in combination with artesunate 50 mg, consistent with the current WHO treatment guidelines for malaria.

A review of this application was prepared by Mr Gray.

The currently recommended dose of this combination from the WHO treatment guidelines is shown below, based on 4 mg/kg body weight artesunate and 10 mg/kg body weight amodiaquine given once daily for 4 days.

Dosing schedule for artesunate + amodiaquine

Age	Dose in mg (No. of tablets)					
	Artesunate (50 mg)			Amodiaquine (153 mg)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5-11 months	25 (½)	25	25	76 (½)	76	76
≥ 1-6 years	50 (1)	50	50	153 (1)	153	153
≥ 7-13 years	100 (2)	100	100	306 (2)	306	306
> 13 years	200 (4)	200	200	612 (4)	612	612

The guidelines also note that this combination is only adequately effective in settings where 28-day cure rates with amodiaquine monotherapy exceed 80%. The lower limit of the dose response curve for amodiaquine efficacy is not considered in the guidelines. Using the proposed fixed-dose combination would potentially be using 88% of the recommended dose of amodiaquine.

The application is based on the regulatory dossier for the product, and presents a total of 15 studies. Five of the studies used a loose combination of artesunate and amodiaquine with a dose ratio of 2.5, and 8 of the studies used a co-blister packed combination of artesunate and amodiaquine with a dose ratio of 3.1. There is one unpublished study using the proposed combination (dose ratio of 2.7) and an additional study is referred to that is complete but not yet analysed. As noted in the expert review, relating these studies to the published literature is not always straightforward (for example, all the WHO/TDR studies were published as a single paper) and there are several published studies that are relevant that may not have been included in this application.

The unpublished study provided by the applicant is Study 5.3.5.1.2, an open randomized controlled trial comparing the FDC artesunate/amodiaquine 25 mg/67.5 mg with a loose combination artesunate 50 mg plus amodiaquine 153 mg. The trial was carried out in Burkina Faso between 2004 and 2006 and was designed as a non-inferiority trial. Subjects were 750 children up to the age of five years with uncomplicated malaria.

In children up to 11 months weighing between 5 and 6.7 kg the dose of the FDC used was 1 tablet per day for 3 days; in the group treated with the loose combination, the dose was half of each table daily. For children aged between 1 and 5 years, weighing 9.2 kg-16.9 kg, the dose was doubled. For children between 6.8 and 9.1 kg, the dose was left to the discretion of the investigator. If any vomiting occurred in the first hour after administration, the dose was repeated. All doses were observed.

The Subcommittee considered an evaluation of the study prepared by the Secretariat and noted that although the study was potentially very important, there were a number of aspects of the quality of the study, as described in the unpublished report, that made it difficult to determine the validity of the results. The Subcommittee also noted that the application refers to an ongoing study of similar design in 941 subjects. The additional features of this second study are that the application specifies that investigating physicians and biologists are blind to treatment allocation. The preliminary presentation of this study was provided by the applicant but a full analysis is not yet complete. If the results of the second study confirm those presented to the Subcommittee, however, it would be evidence of the lower dose of amodiaquine being no worse than the currently recommended dose.

The Subcommittee noted that the quality of the product produced by Sanofi Aventis has been the subject of much discussion. It has been submitted to the WHO Prequalification Programme but has not yet been approved. The application states that one full treatment with the product costs approximately 4 Euros. No assessment of cost-effectiveness is provided.

On balance, the Subcommittee considered that the unpublished study provided substantial support for the clinical equivalence of the proposed FDC and the loose tablets given in currently recommended doses. However, there were some unanswered questions about the study and the results of the second study were not yet available. The Subcommittee decided that, at present, it was not possible to include the product on the EMLc. However, the Subcommittee recommended urgent reconsideration of the clinical data when the results of the second trial were available.

New application: Artesunate + mefloquine fixed-dose combination

At the March 2007 meeting of the Expert Committee, Section 6.5.3.1 of the Model List was comprehensively reviewed. Mefloquine 250 mg tablets are listed for use in combination with artesunate 50 mg, consistent with the current WHO treatment guidelines for malaria. No FDC containing these two components has yet been listed. Co-blistered combinations containing 600/1500, 600/750 and 300/750 mg of artesunate and mefloquine respectively are available. Mepha Ltd. submitted an application for a FDC containing 50 mg artesunate (as pellets) and 125 mg mefloquine (as powder), for use in children weighing 10-20 kg. A review of the application was provided by the Secretariat.

The currently recommended dose of this combination from the WHO treatment guidelines is shown below.

Dosing schedule for artesunate + mefloquine

Age	Dose in mg (No. of tablets)					
	Artesunate (50 mg)			Mefloquine (250 mg)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5-11 months	25 (½)	25	25	–	125 (½)	
≥ 1-6 years	50 (1)	50	50	–	250 (1)	
≥ 7-13 years	100 (2)	100	100	–	500 (2)	250 (1)
> 13 years	200 (4)	200	200	–	1000 (4)	500 (2)

The guidelines note that giving the total dose of 25 mg/kg in a single dose is associated with increased adverse events and therefore recommends the split dose. A recent study *(29)* has examined the acceptability and efficacy of dividing the mefloquine dose into 8 mg/kg per day and has concluded that efficacy remains the same but side-effects are reduced. The guidelines also recommend that lower total doses (i.e. 15 mg/kg) are not as effective as the high dose and therefore should not be used.

Comments were received from the WHO Global Malaria Programme.

The Subcommittee noted that this application is based on the regulatory dossier for the product prepared by Mepha Ltd. and includes a review of published literature. Recent large randomized trials identified by the Secretariat from a limited literature review are not included.

The studies presented in the dossier are four pharmacokinetics studies conducted during the development of the combination, two randomized trials comparing different dosage regimens (evenly split dose of mefloquine versus total dose given on days two and three) and a brief description of five investigator-initiated postmarketing studies. From the summary of the studies provided in the application, it would appear that a total of 41 children weighing between 10 and 20 kg have been treated with the proposed combination (in Study Am-P 001-2005/SPC25-21). The parasite clearance rate or clinical cure in this group was reported to be 100% at 28 days after treatment.

The additional studies *(30-32)* identified by the Secretariat were three large randomized trials comparing artesunate-mefloquine with dihydroartemisin-piperaquine. In these trials both treatments had similar efficacy but there were fewer adverse events with DHA-piperaquine. The standard dose of mefloquine (25 mg/kg over three days) was used in all studies.

The application states that the total exposure to the paediatric preparation since its launch in May 2006 in West Africa is 343 000 children, based on

packs sold and the assumption that each pack is used in one child. Safety data for this group are not provided in detail. The Committee noted that the estimated cost per treatment pack as proposed in the application was US$ 7/pack.

While acknowledging the need for appropriate FDCs for children with malaria, the Subcommittee considered that there is considerable uncertainty with regard to the appropriateness of the dose of mefloquine in this combination. The proposed use is in children from 10-20 kg. A 10 kg child requires 250 mg mefloquine over three days; a 20 kg child requires 500 mg. This combination would overdose a 10 kg child, with the potential risk of adverse events and significantly under dose a child of 20 kg, who would receive 18.75 mg/kg mefloquine. Especially given the relatively narrow therapeutic index of mefloquine, the evidence provided in the application relating to use of this combination is extremely limited and the Committee considered that it did not allow an adequate assessment of either the risk of toxicity in small children (≤ 10 kg) or the risk of inefficacy in larger ones (> 20 kg). In the absence of adequate clinical studies in the target population, the Subcommittee recommended that this combination should not be included in the Model List.

6.5.4 *Medicines for pneumocystis and toxoplasmosis*

The current listing in the 15th EML includes: pyrimethamine, sulfamethoxazole + trimethoprim. ***Complementary List:*** *pentamidine*.

A review of this Section was provided by Dr Deen. There were no applications for additional medicines for this Section.

The Subcommittee endorsed the inclusion of pyrimethamine in the EMLc.

The Subcommittee noted that sulfamethoxazole + trimethoprim is not licensed in the UK for use in children under 6 weeks of age, however the exception is the treatment and prophylaxis of *pneumocystis* pneumonia. The BNF-C (2006) provides doses for both intravenous infusion and oral administration of sulfamethoxazole + trimethoprim for the treatment of *pneumocystis* pneumonia (noting that the oral route is preferred), and doses for oral administration for prophylaxis. Therefore, the Subcommittee endorsed the inclusion of sulfamethoxazole + trimethoprim injection in the EMLc, and added the tablet (sulfamethoxazole + trimethoprim 100 mg + 20 mg, 400 mg + 80 mg) and oral liquid (sulfamethoxazole + trimethoprim 200 mg + 40 mg/5 ml) forms to the EMLc.

The Subcommittee noted that pentamidine was associated with serious side-effects and that in practice the drug was often replaced by other

medicines such as clindamycin. Therefore, the Subcommittee did not endorse the inclusion of pentamidine injection in the EMLc.

6.5.5 *Antitrypanasomal medicines*

The current listing in the 15th EML includes:

6.5.5.1 African trypanosomiasis: For first-stage: pentamidine (*Trypanosoma brucei gambiense* infection), suramin sodium (*Trypanosoma brucei rhodesiense* infection); for second-stage: eflornithine, melarsoprol.

6.5.5.2 American trypanosomiasis: benznidazole, nirfurtimox.

6.5.5.1 African trypanosomiasis

There were no applications for additional medicines for this Section and no additional comments were received.

African trypanosomiasis is a major public health problem in affected countries. Medicines available for treating this infection are limited. Hence despite the toxicity profile, these medicines are still used. There is a paucity of documented information specific to children and recommendations for adults are usually followed.

The Subcommittee acknowledged that there is a lack of information on the effectiveness and safety of these medicines in children, however the seriousness of the illness and experience of their use in the field means that there should be no change in the listing of these medicines. The Subcommittee requested a review of the efficacy and safety of these medicines in children for the next meeting.

The Subcommittee therefore recommended that:

- pentamidine and suramin sodium be endorsed for the EMLc for treatment of first-stage African trypanosomiasis disease (pentamidine for *Trypanosoma brucei gambiense* infection; suramin for *Trypanosoma brucei rhodesiense* infection)
- eflornithine and melarsoprol be endorsed for the EMLc for treatment of second-stage disease.

6.5.5.2 American trypanosomiasis

There were no applications for additional medicines for this Section and no additional comments were received.

The Subcommittee noted that as with treatments for African trypanosomiasis, older drugs are the mainstay of treatment for American trypanosomiasis

(*Trypanosoma cruzi* infection). There is little information on the effectiveness and safety of benznidazole and nifurtimox. The Subcommittee noted a review indicating that the Ministries of Health in Latin America had accepted both agents as specific chemotherapeutic agents for *Trypanosoma cruzi* infection in adults and children, to eliminate the parasite from those infected and for breaking transmission.

The Subcommittee therefore recommended that:

Benznidazole and nifurtimox be endorsed for the EMLc for the treatment of American trypanosomiasis (*Trypanosoma cruzi* infection). The Subcommittee recognized the need to look at the efficacy and safety of these medicines in children for the next meeting. Also there was a need to develop paediatric-appropriate forms of these medicines.

Section 7. Antimigraine medicines

The current listing in the 15th EML includes:

7.1 For the treatment of acute attack: acetylsalicylic acid, paracetamol.

7.2 Prophylaxis: ☐ propranolol.

A review of this Section was prepared by Dr Hoppu. No applications for additional medicines for this Section were submitted. There were a number of additional comments received on the role of ibuprofen and dipyrone for acute migraine attacks, the absence of dose-finding and safety studies of paracetamol in the paediatric population, and the need to limit the number of paracetamol formulations available to avoid medication errors.

The Subcommittee considered the burden of disease of migraine in children, noting that management is similar to that in adults but fewer drugs are approved for treatment of migraine in children.

Acetylsalicylic acid is not recommended for use in children due to the risk of Reye's syndrome. Paracetamol has been shown to be effective for acute migraine attacks, as has ibuprofen, although there are no NSAIDs currently listed on the EML for this indication.

There is conflicting evidence on the efficacy of propranolol in the prevention of migraine in children, but it is the only medicine approved for the prevention of migraine in children.

The Subcommittee therefore recommended that:

1. Acetylsalicyclic acid be deleted from the EMLc for the treatment of acute migraine attacks and ibuprofen tablets 200 mg and 400 mg be added to the EMLc in its place.

2. Paracetamol be endorsed for inclusion in the EMLc for acute migraine attacks.

3. Propranolol be endorsed for inclusion in the EMLc but without a square box listing, in the absence of evidence of effectiveness of other beta blocking agents for prevention of migraine in children.

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

The current listing in the 15th EML includes:

8.1 Immunosuppressive medicines: ***Complementary List:*** *azathioprine, ciclosporin*.

8.2 Cytotoxic drugs: ***Complementary List:*** *asparaginase, belomycin, calcium folinate, chlorambucil, cisplatin, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin, etoposide, fluorouracil, mercaptopurine, methotrexate, procarbazine, vinblastine, vincristine*.

8.3 Hormones and antihormones: ***Complementary List:*** *dexamethasone, hydrocortisone*, □ *prednisolone*, *tamoxifen*.

8.4 Medicines used in palliative care.

Reviews of this Section were prepared by Dr Lie and Dr Ranganathan. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

The importance of access to medicines in this Section was recognized. Furthermore, the need for access to specialist centres was emphasized. The list of immunosuppressants and cytotoxics was thought to be comprehensive. There was agreement that the current list should be retained, even though the evidence for efficacy and safety in children was not reviewed. The medicines should be linked to treatment protocols.

Given the limited information available on the use of azathioprine and ciclosporin in children, the Subcommittee recommended that reviews be commissioned for both drugs for consideration at the next meeting for the

EMLc. Also the committee requested information on the availability of paediatric-appropriate forms.

The cytotoxic drugs (Section 8.2) have been flagged for review at the 16th Expert Committee meeting. The Subcommittee recognized that cytotoxic drugs were essential medicines for children and agreed to include the listing of all of these medicines in the EMLc pending the outcomes of the review. The Subcommittee recognized there were specific malignancies that were relevant to children and recommended that reviews be commissioned to address paediatric priorities, also including review of intrathecal cytotoxic medicines. The Subcommittee agreed that the following malignancies were of importance in children: acute lymphocytic leukaemia, Burkitt lymphoma, Hodgkin and non-Hodgkin lymphoma, Wilms tumour, retinoblastoma, neuroblastoma and Kaposi's sarcoma.

The Subcommittee noted that dexamethasone, hydrocortisone and prednisolone (with square box listing) were included elsewhere in the 15th EML (Section 3, Antiallergics). The Subcommittee recommended that the use of these agents in children be considered as part of the review of Section 8, and suitable paediatric formulations of dexamethasone and prednisolone be identified if clinically appropriate.

Tamoxifen is an estrogen antagonist used for breast cancer therapy and to stimulate ovulation in women with anovulatory infertility. These diseases do not occur in children (or are extremely rare). Therefore the Subcommittee decided to remove tamoxifen from the EMLc.

The Subcommittee endorsed the need for a comprehensive review of medicines for palliative care for children.

Section 10. Medicines affecting the blood

The current listing in the 15th EML includes:

10.1 Antianaemia medicines: ferrous salt, ferrous salt + folic acid, folic acid, hydroxocobalamin.

10.2 Medicines affecting coagulation: heparin sodium, phytomenadione, protamine sulfate, □ warfarin.

Reviews of this Section were prepared by Dr Hoppu and Dr Sachdev. No applications for additional medicines for this Section were submitted.

The Subcommittee accepted the public health need for supplementation with iron and folic acid in children and that vitamin B12 may be required

for deficiency disorders and also for prophylaxis in some situations. Therefore, the Subcommittee agreed to endorse ferrous salt, folic acid and hydroxocobalamin as essential medicines for children. Appropriate formulations of ferrous salts and folic acid need to be included to cover the needs of neonates to adolescents. They should have appropriate excipients for children. While combined therapy with ferrous salts and folic acid is recommended in some settings, the currently listed formulation of 60 mg iron + 400 micrograms folic acid is unlikely to be suitable for children. The Subcommittee proposed a review of the evidence for appropriate dose combinations of iron and folic acid for children for consideration at the next meeting for the EMLc.

The Subcommittee accepted that medicines affecting coagulation were essential for children and endorsed phytomenadione, heparin sodium, protamine sulfate and warfarin (with square box listing) for inclusion in the EMLc. As phytomenadione is routinely administered to neonates, the Subcommittee decided this medicine should be included in the Core List and recommended the addition of phytomenadione injection 1 mg/ml to the list. Because of the need for specialist supervision of the administration of heparin sodium, protamine sulfate and warfarin in children, the Subcommittee recommended that these three medicines be included in the Complementary List for Section 10.2. The Subcommittee recommended the addition of warfarin 0.5 mg tablets to the EMLc.

Section 11. Blood products and plasma substitutes

The current listing in the 15th EML includes:

11.1 Plasma substitutes: ☐ dextran 70 with a note that polygeline injectable solution 3.5% is considered equivalent to dextran 70 injectable solution 6%.

11.2 Plasma fractions for specific use: ***Complementary List:*** *Human normal immunoglobulin (IM and IV formulations)*, ☐ *factor VIII concentrate*, ☐ *factor IX complex (coagulation factors II, VII, IX, X) concentrate*.

Section 11.1 Plasma substitutes

Reviews of this Section were prepared by Dr Hoppu and Dr Sachdev. No applications were received for the addition of medicines to this Section. Comments were received as listed in Appendix 6.

The Subcommittee noted comments suggesting that dextran was considered not to be of use in paediatrics in Europe. Given the concerns expressed

about the role of colloids versus crystalloids in the management of volume depletion, and concerns about the potential for fluid overload in children, the Subcommittee decided not to include dextran in the EMLc and request a review of the existing literature on efficacy and safety of dextran in children for consideration for the EMLc at the next meeting.

Section 11.2 Plasma fractions for specific use (Complementary List)

A review of this Section was prepared by Mrs Al-Fannah. An application was received to add a subcutaneous formulation of human normal immunoglobulin for the treatment of primary immunodeficiencies in adults and children.

The Subcommittee recognized that plasma fractions are essential medicines for both adults and children and endorsed the inclusion of factor VIII concentrate (with square box listing), and factor IX complex (coagulation factors II, VII, IX, X) concentrate (with square box listing) in the Complementary List of the EMLc. The Subcommittee noted comments that recombinant products of factor XIII and factor IX complex should be used in preference to dried and plasma-derived products. These products would be covered by the existing square box listings.

The Subcommittee considered the application to list a subcutaneous formulation of polyvalent human normal immunoglobulin. The specific evidence relating to subcutaneous administration was assessed alongside the detailed application for the listing of the intramuscular and intravenous forms of human normal immunoglobulin considered at the Expert Committee meeting in March 2007. The Subcommittee accepted that while the burden of disease in children was likely to be low, data supported the benefits of treatment of primary immunodeficiency disorders with human normal immunoglobulin on morbidity and survival.

The main trial evidence provided in support of listing of the subcutaneous human normal immunoglobulin (SCIg) was Study SCIG01 describing an open label study of SCIg therapy in 50 patients (15 aged <12 years, 7 aged 12-20 years, 28 adults) previously stabilized on either SCIg or IVIg therapy. Efficacy and safety short-term was assessed as well as long-term effectiveness, tolerability and patient acceptability.

Mean IgG levels increased and were maintained above pre-treatment levels for at least 36 months of therapy. There was no marked increase in frequency, severity or seriousness of bacterial infections prior to and during SCIg therapy; most patients preferred SCIg to their previous therapy and there was no difference between patients previously treated with SCIg and

IVIg. No clinically relevant changes in haematology or biochemistry related to SCIg were reported.

Several appendices to the application cited other observational studies and a review of SCIg therapy, all of which supported the efficacy and safety of SCIg therapy as an alternative to IVIg therapy. Patient satisfaction and quality of life have also been assessed, with the majority of patients preferring SCIg home-based therapy.

The Subcommittee accepted that the evidence presented in the application supports the claims of efficacy and safety of polyvalent human immunoglobulin for subcutaneous administration and it appears to offer some advantages in patient/carer convenience over IVIg therapy and where there are venous access problems. The Subcommittee therefore endorsed the inclusion of human normal immunoglobulin for subcutaneous use (subcutaneous administration of 15%, 16% protein solution) for the treatment of primary immunodeficiency disorders in the EMLc.

Section 12. Cardiovascular medicines

Expert reviews of this Section were provided by Professor Cranswick and Mrs Al-Fannah.

The current listing in the 15th EML includes:

12.1 Antianginals: ☐ atenolol, glyceryl trinitrate, ☐ isosorbide dinitrate, verapamil.

12.2 Antiarrythmic medicines: ☐ atenolol, digoxin, epinephrine, lidocaine, verapamil. ***Complementary List:*** *procainamide, quinidine*.

12.3 Antihypertensive medicines: ☐ amlodipine, ☐ atenolol, ☐ enalapril, hydralazine, ☐ hydrochlorothiazide, methyldopa. ***Complementary List:*** *sodium nitroprusside*.

12.4 Medicines used in heart failure: digoxin, ☐ enalapril, ☐ furosemide, ☐ hydrochlorothiazide. ***Complementary List:*** *dopamine*.

12.5 Antithrombotic medicines: acetylsalicylic acid. ***Complementary List:*** *streptokinase*.

12.6 Lipid-lowering agents: ☐ simvastatin.

The Subcommittee decided that antianginal medicines were not required in children and agreed to delete Section 12.1 medicines from the EMLc.

The Subcommittee noted that congenital heart disease in children in particular is a problem requiring essential medicines. However, without having detailed evidence of the efficacy and safety of the medicines listed in Section 12 as antiarrhythmic medicines, antihypertensive medicines, antithrombotic medicines and lipid-lowering medicines, it could not endorse any of the currently listed items as essential. It therefore requested a review of the use of these medicines in children for the next meeting.

For management of heart failure in children, the Subcommittee endorsed the inclusion of digoxin (injection, tablet and liquid forms), and furosemide (injection and tablet forms) in Section 12.4 (Medicines used in heart failure) with the addition of an oral liquid form of furosemide (20 mg/5 ml). Enalapril was noted to be not licensed for use in children and therefore not endorsed at this time. Dopamine was also endorsed for inclusion on the Complementary List of medicines, but the Subcommittee requested a review of other medicines used as inotropes in children for its next meeting.

Section 13. Dermatological medicines (topical)

The current listing in the 15th EML includes:

13.1 Antifungal medicines: benzoic acid + salicylic acid, ☐ miconazole, sodium thiosulfate. ***Complementary List:*** *selenium sulphid*e.

13.2 Anti-infective medicines: ☐ methylrosaninium chloride (gentian violet), neomycin + ☐ bacitracin, potassium permanganate, silver sulfadiazine.

13.3 Anti-inflammatory and antipruritic medicines: ☐ betamethasone, ☐ calamine lotion, ☐ hydrocortisone.

13.4 Astringent medicines: aluminium diacetate.

13.5 Medicines affecting skin differentiation and proliferation: benzoyl peroxide, coal tar, dithranol, fluorouracil, ☐ podophyllum resin, salicyclic acid, urea.

13.6 Scabicides and pediculicides: ☐ benzyl benzoate, permethrin.

Reviews of various parts of this Section were provided by Dr Jeena, Dr Sri Ranganathan and Dr Dai. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

Section 13.1 Antifungal medicines

The Subcommittee endorsed the inclusion of benzoic acid + salicylic acid, miconazole (with square box listing) and selenium sulphide detergent-based suspension on the EMLc.

The Subcommittee noted that the clinical effectiveness of sodium thiosulfate has not been established. It appears to have fungistatic action and has been used in the treatment of pityriasis versicolor, however there are better options now available. The Subcommittee therefore decided not to include sodium thiosulfate in the EMLc.

Section 13.2 Anti-infective medicines

The Subcommittee noted that methylrosanilinium chloride (gentian violet) has antifungal and antibacterial activity and is useful for minor infections on the skin and for oral and vaginal candidiasis. While there are better options available now, this preparation may still be useful in resource-poor settings. The Subcommittee noted that the use of neomycin + bacitracin over large areas of skin can lead to systemic toxicity (ototoxicity and nephrotoxicity). Similarly, the application of silver sulfadiazine cream over large areas of skin can also be associated with systemic toxicity (due to sulphonamides).

The Subcommittee endorsed the inclusion of methylrosaninium chloride (gentian violet) (with square box listing) but recognized that its role would be reviewed at the next meeting as new trials are currently being conducted on its use. Neomycin + bacitracin (with square box listing for bacitracin), and silver sulfadiazine cream were endorsed for the EMLc with some concerns expressed about their use in newborns. The Subcommittee also endorsed the inclusion of potassium permanganate for the list. The Subcommittee recognized that polyvidone iodine topical formulations (10% ointment) should be reviewed and considered for addition to the list.

Section 13.3 Anti-inflammatory and antipruritic medicines

The Subcommittee endorsed the inclusion of betamethasone (with square box listing), with a warning about the use of more potent topical steroids in small children. Calamine lotion (without square box listing) and hydrocortisone (without square box listing) were endorsed for inclusion in the EMLc.

Section 13.4 Astringent medicines

The Subcommittee noted that there were no clear indications for the use of aluminium diacetate topical solution 5% in children. While there were no specific safety issues with its use in children identified, the Subcommittee

decided not to include aluminium diacetate topical solution in the EMLc. There should be a review of the need for an astringent preparation for the next meeting.

Section 13.5 Medicines affecting skin differentiation and proliferation

The Subcommittee endorsed the inclusion of benzoyl peroxide, coal tar, dithranol, podophyllum resin (with square box listing), salicylic acid and urea preparations for inclusion in the EMLc. The risks of using salicylic acid in young children were noted.

The Subcommittee noted that there were no clear indications for use of fluorouracil in children and that the product was not licensed for use in children. Therefore the Subcommittee decided not to include fluorouracil in the EMLc.

Section 13.6 Scabicides and pediculicides

The Subcommittee endorsed the inclusion of benzyl benzoate (with square box listing) and permethrin preparations in the EMLc. The age restrictions on use of benzyl benzoate were recognized as a problem, however the addition of these to the Model List at the current time may provide an incentive for further development of preparations suitable for younger children (particularly < 2 years of age). Alternatives for this age group need to be considered for addition to the list.

Section 14. Diagnostic agents

The current listing in the 15th EML includes

14.1 Ophthalmic medicines: fluoroscein, ☐ tropicamide.

14.2 Radiocontrast media: ☐ amidotrizoate, barium sulfate, ☐ iohexol.
Complementary List: ☐ *meglumine iotroxate*.

Reviews of various parts of this Section were provided by Mrs Al-Fannah and Dr Deen. There were no applications for listing of new medicines for this Section.

The Subcommittee noted concerns about the potential side-effects of tropicamide, which can in rare cases cause CNS disturbances that can be harmful to children. The Subcommittee endorsed the inclusion of fluoroscein and tropicamide (with square box listing) in the EMLc.

The Subcommittee noted concerns expressed about the licensing status of barium sulfate and meglumine iotroxate for use in children. Given these medicines are administered in specialized facilities under the supervision of radiologists, the Subcommittee endorsed only the inclusion of barium sulfate at present on the EMLc. The Subcommittee considered that an expert review of this area in relation to the imaging of children should be provided for the next meeting.

Section 15. Disinfectants and antiseptics

The current listing in the 15th EML includes:

15.1 Antiseptics: ☐ chlorhexidine, ☐ ethanol, ☐ polyvidone iodine.

15.2 Disinfectants: ☐ chlorine base compound, ☐ chloroxylenol.

Reviews for this Section were provided by Dr Dai and Dr Kearns. There were no applications for listing of new medicines or products for this Section.

The Subcommittee endorsed the inclusion of chlorhexidine (with square box listing), ethanol (with square box listing) and polyvidone iodine (with square box listing) as antiseptics in the EMLc.

The Subcommittee endorsed the inclusion of chlorine base compound (with square box listing), chloroxylenol (with square box listing) and glutaral as disinfectants in the EMLc. The Subcommittee recognized that the disinfectants were not medicines per se, but the importance of a clean environment where children are treated was seen as a priority and the inclusion of this Section was to emphasize the importance of infection control.

Section 16. Diuretics

The current listing in the 15th EML includes: amiloride, ☐ furosemide, ☐ hydrochlorothiazide, mannitol, spironolactone.

The Subcommittee considered that diuretics were essential for use in children in the treatment of ascites, acute or chronic renal failure or acute glomerulonephritis. Nephrotic syndrome edema responds poorly to diuresis, and loop diuretics may be hazardous because patients are often volume-depleted despite edema.

The Subcommittee considered that furosemide should be listed, and that spironolactone should be listed for use in cirrhosis and heart failure by centres undertaking such treatment.

The Subcommittee considered that spironolactone, hydrochlorothiazide and mannitol should be listed under this Section but moved to the Complementary List. The role of mannitol should be reviewed in light of potential newer agents for the next meeting. The Subcommittee also requested a review of use of spironolactone in children for the next meeting.

Section 17. Gastrointestinal medicines

The current listing in the 15th EML includes

17.1 Antacids and other antiulcer medicines: aluminium hydroxide, ☐ ranitidine, magnesium hydroxide.

17.2 Antiemetic medicines: metoclopramide, promethazine.

17.3 Anti-inflammatory medicines: ☐ sulfasalazine. ***Complementary List:*** ☐ hydrocortisone (with square box listing relating to retention enemas only).

17.4 Laxatives: ☐ senna.

17.5 Medicines used in diarrhoea:
- **17.5.1 Oral rehydration:** oral rehydration salts.
- **17.5.2 Medicines for diarrhoea in children:** zinc sulfate.
- **17.5.3 Antidiarrhoeal (symptomatic) medicines in adults:** codeine.

Section 17.1 Antacids and other antiulcer medicines

A review of this Section was prepared by Professor Cranswick. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

The Subcommittee endorsed aluminium hydroxide, magnesium hydroxide and ranitidine (with square box listing) for inclusion in the EMLc. It also requested a review of proton pump inhibitors in children.

Section 17.2 Antiemetic medicines

A review of this Section was prepared by Dr Lie. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

The Subcommittee noted the concerns expressed about potential side-effects of metoclopramide in children who are particularly susceptible to induced acute dystonic reactions. The Subcommittee endorsed metoclopramide for inclusion in the EMLc with a note that it is not for use in neonates. A review

of domperidone was requested. The Subcommittee also requested a review and preparation of an application for the inclusion of a 5-HT3 antagonist as an alternative to metoclopramide for the next meeting.

The Subcommittee endorsed the inclusion of promethazine in the EMLc, but added a note indicating that promethazine was "contraindicated in children under 2 years".

Section 17.3 Anti-inflammatory medicines

The Subcommittee considered this group of medicines and decided that on epidemiological grounds, there was no need to include this Section in the EMLc at present.

Section 17.4 Laxatives

A review of this Section was prepared by Dr Lie. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

The Subcommittee accepted that the use of senna in children was limited and noted comments that liquid paraffin and lactulose may be preferred laxatives for use in children. Therefore the Subcommittee decided not to list any laxatives on the EMLc at this time and to request a review of an alternative laxative for use in children for consideration at the next meeting for the EMLc.

Section 17.5 Medicines used in diarrhoea

Reviews of this Section were prepared by Dr Lie and Dr Sachdev. There was an application for racecadotril to be listed in this Section. Additional comments were received and considered by the Subcommittee.

The Subcommittee endorsed the listing of oral rehydration salts and zinc sulphate on the EMLc. The Subcommittee noted and discussed that the quality and availability of zinc sulfate preparations were a concern. The Subcommittee agreed that a dispersible tablet formulation is more useful because most patients are below the age of 2 years. While it is the zinc sulfate salt that is listed, alternative zinc salts and forms may also be available and the status of zinc should be reviewed for the next meeting.

The Subcommittee noted the paper from Dr Olivier Fontaine of the Child and Adolescent Health Department, WHO, regarding the footnote to oral rehydration salts in the 15th EML. Based on the results of studies conducted in Bangladesh and India, there appears to be only a minimal risk of symptoms associated with hyponatraemia in patients (adult and children) treated with reduced osmolarity ORS and the risk did not appear to increase

with a change in formulation. Therefore, the Department believes that the footnote "In cases of cholera a higher concentration of sodium may be required" is no longer required. The Subcommittee agreed to delete the footnote to oral rehydration solution in the EMLc.

The Subcommittee agreed that Section 17.5.3 (medicines in adults) was not relevant for the EMLc and should be deleted.

New application: Racecadotril

The Subcommittee considered an application for the listing of a new medicine, racecadotril. Racecadotril (acetorphan) is an enkephalinase inhibitor with antisecretory and antidiarrhoeal actions, to be used in conjunction with oral rehydration salts for the treatment of watery diarrhoea. It exerts its antidiarrhoeal effects by preventing the breakdown of endogenous enkephalins in the gastrointestinal tract. The key evidence on effectiveness of racecadotril was derived from two randomized controlled trials *(33, 34)*.

Expert reviews were prepared by Dr Sri Ranganathan and Dr Sachdev. Additional comments were received from the WHO Department of Child and Adolescent Health not supporting the addition.

The trial by Salazar-Lindo was conducted in 135 boys (3-35 months of age) hospitalized because of dehydration (watery diarrhoea for less than 5 days, ≥ 3 diarrhoeic stools in the 24 hours before hospital admission). The study compared ORT + placebo and ORT + racecadotril (1.5 mg/kg) administered eight-hourly. The primary outcome assessed was stool output in the first 48 hours. The mean (±SE) 48 hour stool output was 92±12 g per kg in the racecadotril group compared to 170±15 g per kg in the placebo group. The 46% lower output with racecadotril was statistically significant ($P < 0.001$). In addition, there was a statistically significantly lower total stool output and a shorter duration of diarrhoea in the racecadotril group. Results were similar in rotavirus positive and negative boys. The overall 5-day cure rates were 84% in the racecadotril group and 66% in the placebo group. Lower total intake of ORT was reported in the racecadotril group.

The second trial (Cezard et al.) was conducted in France and involved 172 children (71 girls, 101 boys aged 3 months to 4 years) hospitalized for severe acute diarrhoea (watery diarrhoea with ≥ 3 watery stools per day of less than 72 hours duration). ORT was administered ad libitum each hour for the first 24 hours of the study either orally or by gastric tube, with 50% of the total amount given within the first 6 hours. Racecadotril was administered in a dose of 1.5 mg/kg three times daily. The primary outcome assessed was stool output (grams per hour) during the first 48 hours. There

was a statistically significant reduction in stool output in the racecadotril group in the full data set, with an approximate 40% reduction compared to placebo, with no evidence of differences in male and female infants or by rotavirus status. Similar results were observed in the per-protocol analysis. There was a statistically significant reduction in stool output within 24 hours in the racecadotril group (secondary outcome). Recovery rates within 5 days were similar in both treatment arms of the study (88% male, 79% females receiving racecadotril versus 90% male, 82% female infants in the placebo group), although most patients had recovered before 5 days.

Tolerability was assessed in both of the trials. Racecadotril was generally well tolerated and no serious adverse effects attributable to the medicine were reported. The application also provides some data from post-marketing pharmacovigilance activities which suggest that the most frequent adverse events with racecadotril were cutaneous and/or allergic (i.e. rash, erythematous/papulous reaction, prurigo and urticaria).

Both of these studies suggest a benefit of racecadotril therapy as an adjunct to ORT in reducing stool output in subjects with severe diarrhoea/dehydration. However, both studies were conducted in hospital settings and under rigorous trial conditions and it is difficult to generalize the results of the study to assess the value of racecadotril therapy out of hospital settings, and in less severely affected infants. It is unclear whether the more complex regimen (needing to administer both ORT and racecadotril) will compromise treatment effectiveness in real-life settings. Experience with the use of racecadotril remains limited with only 307 infants participating in the two trials cited in the application.

The Subcommittee noted that racecadotril represents an entirely new class of agent for the management of diarrhoea in children. Given the problem of adequately treating diarrhoea, it is important that treatment regimens used are simple, safe and of demonstrated effectiveness in a variety of clinical settings. The Subcommittee decided that as yet there are insufficient clinical data to support the inclusion of racecadotril in the EMLc. There is a clear need for further studies to determine clinical effectiveness and safety and to assess the feasibility and acceptability of treatment regimens that involve administration of two sachet formulations.

Section 18. Hormones, other endocrine medicines and contraceptives

The current listing in the 15th EML includes: Sections 18.1 (Adrenal hormones and synthetic substitutes), 18.2 (Androgens), 18.3 (Contraceptives),

18.4 (Estrogens), 18.6 (Ovulation inducers) and 18.7 (Progestogens). Not all of these Sections are relevant to children aged under 12 years.

18.1 (Adrenal hormones and synthetic substitutes):

The Subcommittee felt that this area should be included on the EMLc under the complementary Section and reviewed with inclusion of a proposal for fludrocortisone for the next Subcommittee meeting.

18.5 Insulin and other antidiabetic agents: glibenclamide, insulin injection (soluble), intermediate acting insulin, metformin.

18.8 Thyroid hormones and antithyroid medicines: levothyroxine, potassium iodide, ☐ propylthiouracil.

Reviews for this Section were provided by Dr Hoppu and Mrs Al-Fannah. There were no applications for listing of new medicines for this Section; no other comments were received.

The Subcommittee endorsed the inclusion of insulin injection (soluble) and intermediate-acting insulin in the EMLc. The Subcommittee noted the need to develop age-appropriate devices for administration of insulins in children.

There is an emerging need for oral antidiabetic drugs suitable for children due to the increasing obesity epidemic and increasing Type II diabetes in children. The Subcommittee noted that glibenclamide and metformin were still primarily used in adult populations for Type II diabetes. The potential need of these medicines in adolescents and children was recognized. The Subcommittee decided not to include glibenclamide in the EMLc at present. The Subcommittee decided to include metformin in the EMLc on the Complementary List. This area should be reviewed at a subsequent meeting taking into account available medicines and the changing epidemiology of Type II diabetes in children under 12 years.

The Subcommittee endorsed the inclusion of levothyroxine in the EMLc and recommended the addition of 25 microgram tablets. The Subcommittee also identified the need for a form appropriate for neonates and young children.

The Subcommittee discussed the addition of Lugol's solution (about 130 mg total iodine/ml) in addition to the existing 60 mg tablets of potassium iodide. The Subcommittee endorsed the inclusion of Lugol's solution and potassium iodide tablets in the EMLc.

The Subcommittee noted that propylthiouracil is licensed for use in children aged over 6 years, although in some settings carbimazole is the more commonly used drug. The Subcommittee decided to list propylthiouracil

in the EMLc at present but have the role of carbimazole reviewed for the next meeting.

Section 19. Immunologicals

The current listing in the 15th EML includes:

19.1 Diagnostic agents: tuberculin, purified protein derivative.

19.2 Sera and immunoglobulins: anti-D immunoglobulin (human), antitetanus immunoglobulin (human), antivenom immunoglobulin (exact type to be defined locally), diphtheria antitoxin, ☐ rabies immunoglobulin.

19.3 Vaccines: BCG vaccine, cholera vaccine, diphtheria vaccine, hepatitis A vaccine, hepatitis B vaccine, *Haemophilus influenzae* type b vaccine, influenza vaccine, Japanese encephalitis vaccine, measles vaccine, meningococcal meningitis vaccine, mumps vaccine, pertussis vaccine, pneumococcal vaccine, poliomyelitis vaccine, rabies vaccine, rotavirus vaccine, rubella vaccine, tetanus vaccine, typhoid vaccine, varicella vaccine, yellow fever vaccine.

Reviews of this Section were prepared by Dr Dai and Dr Deen. There were no new applications for additions to this Section.

The Subcommittee endorsed tuberculin, purified protein derivative for listing on the EMLc.

The Subcommittee decided to delete anti-D immunoglobulin (human) from Section 19.2 as it is not indicated for use in children. All other sera and immunoglobulins in Section 19.2 were endorsed for listing in the EMLc.

Given the review of Section 19.3, Vaccines, at the 15th Expert Committee meeting in March, the Subcommittee endorsed all current listings under 19.3 for inclusion in the EMLc.

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

The current listing in the 15th EML includes:

20. Muscle relaxants: ☐ alcuronium, neostigmine, suxamethonium. ***Complementary List***: *pyridostigmine*, ☐ *vecuronium*.

Reviews for this Section were provided by Professor Cranswick and Dr Sri Ranganathan. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

The Subcommittee noted that alcuronium was an older drug that had largely been superseded by other non-depolarizing muscle relaxants. Alternatives to this include vecuronium (in the Complementary List) and atracurium. The Subcommittee decided to retain vecuronium, with a square box listing with selection based on availability and relative cost. The Subcommittee decided not to list alcuronium.

The Subcommittee noted that neostigmine metisulfate injection was the preferred agent for the reversal of non-depolarising muscle block and endorsed neostigmine injection for inclusion in the EMLc. While neostigmine bromide tablets are licensed for use in infants and children for the treatment of myasthenia gravis, the Subcommittee noted that pyridostigmine has fewer cholinergic adverse effects and is now regarded as the first-line drug treatment for myasthenia gravis. The Subcommittee endorsed neostigmine (injection and tablet forms) and pyridostigmine (injection and tablet forms) for inclusion in the EMLc, with the latter retained in the Complementary List.

The Subcommittee endorsed suxamethonium for inclusion in the EMLc.

Section 21. Ophthalmological preparations

The current listing in the 15th EML includes:

21.1 Anti-infective agents: aciclovir, ☐ gentamicin, ☐ tetracycline.

21.2 Anti-inflammatory agents: ☐ prednisolone.

21.3 Local anaesthetics: ☐ tetracaine.

21.4 Miotics and antiglaucoma medicines: acetazolamide, ☐ pilocarpine, ☐ timolol.

21.5 Mydriatics: atropine. ***Complementary List:*** *epinephrine (adrenaline)*.

Reviews of this Section were provided by Professor Cranswick and Mr Gray. There were no applications for listing of new medicines for this Section.

The Subcommittee endorsed the listing of aciclovir, gentamicin (with square box listing) and tetracycline (with square box listing) eye preparations for inclusion in the EMLc.

The Subcommittee noted comments on the need for topical ophthalmic steroids to be administered under expert supervision to avoid inadvertent use in herpes simplex infections. The Subcommittee endorsed the inclusion of prednisolone eye drops with a square box listing.

The Subcommittee endorsed the listing of tetracaine (with square box listing) eye preparation for inclusion in the EMLc, with an age warning to avoid use in preterm neonates.

The Subcommittee accepted that glaucoma was rare in children and did not include this group of medicines in the current EMLc.

The Subcommittee endorsed inclusion of atropine eye drops on the EMLc. The Subcommittee recognized the risk of systemic effects with atropine eye drops in infants under 3 months. The Subcommittee decided to delete the square box and nominate homatropine and cyclopentolate as alternative mydriatic preparations for use in children.

The Subcommittee endorsed the listing of epinephrine (adrenaline) eye drops in the Complementary List for Section 21.5.

The Subcommittee discussed the ophthalmological preparations suggested as possible inclusions in Section 21 at the 15th Expert Committee Meeting in March 2007. The Subcommittee agreed on the importance of identifying preparations relevant to children and that these should be priority targets for reviews and formal applications to the Committee.

Section 23. Peritoneal dialysis solution

Section 23 lists: intraperitoneal dialysis solution (of appropriate composition) in the ***Complementary List.***

A review was provided by Dr Jeena. There were no applications for additional medicines for this Section and no additional comments were received.

The Subcommittee recognized that the need for peritoneal dialysis solution in children would be very low, and that it would be used for acute rather than chronic dialysis. The Subcommittee endorsed the inclusion of peritoneal dialysis solution in the EMLc (Complementary List). The existing listing (of appropriate composition) would cover hypo-, iso- and hypertonic glucose solutions. The Subcommittee emphasized the need for manufacturers to consider providing peritoneal dialysis bags of appropriate volume for use in children, according to the size of the child, for example 500 ml or 1000 ml.

Section 24. Psychotherapeutic medicines

The current listing in the 15th EML includes:

24.1 Medicines used in psychotic disorders: ☐ chlorpromazine, ☐ fluphenazine, ☐ haloperidol.

24.2 Medicines used in mood disorders.

24.2.1 Medicines used in depressive disorders: ☐ amitriptyline, fluoxetine.

24.2.2 Medicines used in bipolar disorders: carbamazepine, lithium carbonate, valproic acid.

24.3 Medicines used in generalized anxiety and sleep disorders: ☐ diazepam.

24.4 Medicines used for obsessive compulsive disorders and panic attacks: clomipramine.

A review of this Section was provided by Dr Jeena. There were no applications for listing of new medicines for this Section. Comments were received as listed in Appendix 6.

Section 24.1 Medicines used in psychotic disorders

The Subcommittee noted that there is little information on the efficacy and safety of antipsychotic drugs in children and adolescents and much of the information available has been extrapolated from adult data. The Subcommittee recognized that chlorpromazine is still widely used despite the wide range of adverse effects associated with it, and that while it has marked sedating effects, it may be useful for treating violent children without causing stupor. The Subcommittee endorsed the inclusion of chlorpromazine injection and 100 mg tablets in the EMLc, recommended the addition of 10 mg, 25 mg and 50 mg tablets and retained the oral liquid formulation of chlorpromazine. The Subcommittee decided to list chlorpromazine without a square box.

The Subcommittee noted that fluphenazine was not licensed for use in children and decided not to list fluphenazine in the EMLc at this time and to seek a review of alternative antipsychotics for use in children.

The Subcommittee decided to include haloperidol in the EMLc at this time, but without a square box listing and without an age restriction. The Subcommittee decided to add haloperidol 0.5 mg tablets and liquid form (2 mg/ml). The Subcommittee also requested a review of appropriate antipsychotics for use in children including risperidone.

Section 24.2 Medicines used in mood disorders

24.2.1 *Medicines used in depressive disorders*

The Subcommittee noted that while depression in children is widely recognized, there is controversy about the role of drug treatment in children

and the balance of benefits and harms of therapy. The safety and efficacy of tricyclic antidepressant drugs in the treatment of depression in children have not been established.

Because of a lack of evidence of efficacy of tricyclic antidepressants in children under 12 years, the Subcommittee decided not to include amitriptyline in the EMLc.

The Subcommittee noted the comments of regulatory and safety authorities on the use of SSRIs (selective serotonin reuptake inhibitors) in children. In making their decision, the Subcommittee took the following into account:

- the recent application considered by the Expert Committee in March 2007 had included data on the efficacy and safety of fluoxetine when used by patients under 18 years of age
- that there were discrepancies in the minimum age approved by a number of regulatory authorities.

The Subcommittee therefore endorsed the inclusion of fluoxetine in the EMLc with an age restriction of > 8 years.

24.2.2 *Medicines used in bipolar disorders*

The Subcommittee decided not to list any medicines in the EMLc for the management of bipolar disorder at this time, but to seek a review of the management of bipolar disorder in children.

Section 24.3 Medicines used in generalized anxiety and sleep disorders

The Subcommittee considered the need for medicines for the management of generalized anxiety and sleep disorders in children and decided that this Section needs review for the next meeting.

Section 24.4 Medicines used for obsessive compulsive disorders and panic attacks

The Subcommittee decided not to list any medicines in the EMLc for the management of obsessive compulsive disorder and panic attacks at this time, but to seek a review of the management of these conditions in children.

Section 25. Medicines acting on the respiratory tract

The current listing in the 15th EML includes:

25.1 Antiasthmatic and medicines for chronic obstructive pulmonary disease: ☐ beclometasone, epinephrine (adrenaline), ipratropium bromide, ☐ salbutamol.

25.2 Other medicines acting on the respiratory tract: caffeine citrate.

Reviews for parts of this Section were provided by Dr Peterson, Mr Gray and Professor Cranswick. There were no applications for additional medicines for this Section.

The Subcommittee agreed that chronic obstructive pulmonary disease was a disease of adults and not children and therefore to change the Section 25.1 heading to 'Antiasthmatic medicines'.

The Subcommittee identified that the budesonide inhaler should replace beclometasone on the EMLc as it is more widely registered for use in children. The Subcommittee endorsed the listing of the current available inhalers with a square box listing.

The Subcommittee endorsed the inclusion of epinephrine (adrenaline) but not ipratropium bromide in the EMLc as there is uncertainty as to its role in childhood asthma and required review.

The Subcommittee endorsed the inclusion of salbutamol (with square box listing) in the EMLc. The Subcommittee recognized that salbutamol tablets and syrup formulations are rarely used in managing childhood asthma in a number of countries. The Subcommittee included the tablet and oral liquid forms on the list but requested a review of the evidence for the use of these forms (especially in young children with viral-related wheeze) for the next meeting of the Subcommittee. There was also a request to include a review of long-acting beta2-agonists in children.

The Subcommittee endorsed the inclusion of caffeine citrate in the EMLc. There was recognition that countries may have difficulty in sourcing caffeine; aminophylline has equivalent efficacy but its safety profile is less favourable and it required therapeutic drug monitoring.

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

The current listing in the 15th EML includes:

26.1 Oral: oral rehydration salts (See Section17.5.1), potassium chloride.

26.2 Parenteral: glucose, glucose with sodium chloride, potassium chloride, sodium chloride, sodium hydrogen carbonate, □ sodium lactate compound solution.

26.3 Miscellaneous: water for injection.

A review of this Section was provided by Dr Sachdev. There were no applications for additional medicines for this Section and no additional comments were received.

The Subcommittee endorsed the inclusion of oral rehydration salts and potassium chloride in the EMLc. The footnote in Section 17.5.1 under oral rehydration salts has been removed.

The Subcommittee endorsed the inclusion of glucose, glucose with sodium chloride, potassium chloride, sodium chloride, sodium hydrogen carbonate and sodium lactate compound solution (with square box listing) in the EMLc. The Subcommittee endorsed the addition of two additional strengths of glucose and sodium chloride solution (5% glucose, 0.9% sodium chloride and 5% glucose, 0.45% sodium chloride). The Subcommittee endorsed the listing of water for injection on the EMLc.

Section 27. Vitamins and minerals

The current listing in the 15th EML includes:

27. Vitamins and minerals: ascorbic acid, ☐ ergocalciferol, iodine, ☐ nicotinamide, pyridoxine, retinol, riboflavin, sodium fluoride, thiamine. ***Complementary List:*** *calcium gluconate*.

Reviews on this Section were provided by Dr Sachdev and Dr Sri Ranganathan. There were no applications for additional medicines for this Section and no additional comments were received.

The Subcommittee endorsed the inclusion of ascorbic acid on the EMLc. The Subcommittee discussed the need for a higher strength tablet of ascorbic acid, but decided not to add another formulation at this time.

The Subcommittee discussed the suggestion of adding cholecalciferol to ergocalciferol in appropriate, equivalent forms and dosages because of the better bioavailability and metabolic action of cholecalciferol. The Subcommittee agreed to endorse both cholecalciferol and ergocalciferol for listing in the EMLc.

The Subcommittee endorsed the inclusion of iodine formulations in the EMLc.

The Subcommittee noted comments that most of the listed indications for nicotinamide, including nicotinamide deficiency, are now rare in children and therefore the Subcommittee decided not to include nicotinamide in the EMLc but to review this as part of the review of the Section.

The Subcommittee endorsed the inclusion of pyridoxine, retinol and riboflavin on the EMLc.

The Subcommittee endorsed the inclusion of sodium fluoride on the EMLc. The Subcommittee noted that sodium fluoride is contraindicated in regions with fluorosis or where the water is fluoridated.

The Subcommittee endorsed the inclusion of thiamine tablets on the EMLc.

The Subcommittee endorsed the inclusion of calcium gluconate injection in the EMLc (Complementary List). The Subcommittee discussed the need to include an oral preparation of calcium for use in children. The Subcommittee agreed that there was a need for a review of the evidence on the efficacy, safety and appropriate doses and formulations of oral calcium as well as magnesium and phosphate for use in children.

The Subcommittee considered several other issues in relation to Section 27, including the need for syrup or liquid formulations for all micronutrients and minerals; the need to include magnesium and phosphate supplements in the EMLc; the need for a vitamin B12 preparation given the emerging data about vitamin B12 deficiency; the need for a multivitamin preparation in the EMLc; and the effectiveness and appropriate formulations of vitamins for use in premature infants and children with severe malnutrition, malaria and HIV/AIDS. The Subcommittee agreed that these were important issues, and recognized that this Section needs revision as a high priority. All of the essential vitamins and minerals should be available in forms suitable for dosing young children.

5. Summary of recommendations

Needs identified

The Subcommittee identified a number of specific areas for further research and medicines development to address the medicines needs of children.

General issues:

1. need for small tablet sizes, suitable for administration to children
2. recognition of new technologies in formulating medicines for children (e.g. microencapsulation techniques)
3. standardized delivery forms for liquids for children
4. age-appropriate devices for drug delivery to infants and children

Specific dosage forms of individual medicines:

1. morphine injection 1 mg/ml
2. age-appropriate fixed-dose combinations for children for the treatment of malaria and TB
3. formulation and salts of zinc
4. rifampicin, ethambutol, isoniazid in paediatric dosage forms
5. aciclovir — dispersible tablet form
6. didanosine — buffered powder formulation was identified as a particular problem
7. stavudine syrup — current preparation is an inappropriate strength and requires refrigeration
8. nevirapine sachet formulation (for Preventing Mother-to-Child Transmission (pMTCT) programmes)
9. ritonavir syrup formulation (current formulation has taste/ administration issues)
10. chloroquine liquid form (palatability issue)
11. mefloquine liquid form
12. pyrimethamine in liquid form
13. peritoneal dialysis solution — smaller bags of 500 ml or 1000 ml
14. dispersible tablet formulation of albendazole
15. benznidazole syrup or lower-strength tablet

Research needs:

1. ototoxicity of gentamicin

Information needs:

1. identification of existing paediatric dose forms at a global level
2. repository of information on extemporaneous preparations (formulation and stability information etc.).

Gaps identified

In addition, the Subcommittee identified a number of gaps in the EMLc which required urgent attention:

- ENT medicines
- behavioural disorders in children (including attention deficit hyperactivity disorder, autism)
- medicines for resuscitation
- medicines to manage iatrogenic 'events'
- medicines for neonates
- medicines for the management of the metabolic and neurological complications of HIV and its treatment.

Priorities for reviews

The Subcommittee considered a list of reviews that were identified during the meeting (see Appendix 6). From this list, the Subcommittee identified the following priority areas:

- medicines for TB in appropriate paediatric formulations, both single agents and fixed-dose combinations
- multivitamin preparations for use in children with malnutrition and HIV
- fixed-dose combinations for HIV in appropriate paediatric formulations
- medicines for pain in children, including ibuprofen
- a 5HT3 antagonist
- other anti-infectives
- medicines for neonates.

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Appendix 1

Declaration of interests of Subcommittee Members

The Members of the Subcommittee reported the following:

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

Mr Andy Gray reported having accepted travel support and honoraria from AstraZeneca, Aspen Pharmacare, Alphapharm for continuing professional development lectures; research support from the Merck Foundation (2002), 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 GSK Finland (2004) and Leiras Ltd Finland (2005). 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.

Professor Prakash Mohan Jeena declared being a principal investigator on a planned but not yet commenced trial of protease inhibitors in HIV (GSK) and receiving travel support and honoraria for lectures from GSK, Wyeth, MSD, BMS, Sandoz and Abbott.

Dr Peter Kazembe, Dr Helena Coelho and Mrs Jehan Mohammed Ali Al-Fannah reported no conflict of interest.

The Temporary Advisers reported the following:

Dr Gregory Kearns reported research support for pharmacokinetics studies from Wyeth Pharmaceuticals, Astellas Pharma USA, Cubist Pharmaceuticals, Amylin Pharmaceuticals, and GlaxoSmithKline. In addition, Dr Kearns has done consultancy work for Proctor and Gamble, BioDelivery Sciences, Merck, Altana Pharma, Morton Grove Pharmaceuticals, Cubist Pharmaceuticals and Abbott Laboratories. He also serves as a member of the United States FDA Clinical Pharmacology

Advisory Committee and receives research support from the National Institutes of Health.

Dr Stuart Macleod reported having been a part owner of i3Innovus, a contract research organization providing consultancy advice in pharmacoepidemiology and health economics until Feb 2006, but without direct interest in any products; and being Executive Director of the Child and Family Research Institute, University of British Columbia, which holds research contracts with the private sector, but is not PI on any of these contracts.

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

Professor Dai Yao Hua, Dr Sverre Lie, Dr William Rodriguez, Dr Shalini Sri Ranganathan, Dr Robert Peterson and Professor H. P. S. Sachdev reported no conflict of interest.

Dr Jacqueline Deen 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.

Appendix 2

WHO Model List of Essential Medicines for Children

Explanatory Notes

This Model List is intended for use for children up to 12 years of age.

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

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

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

Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price. Medicines are listed in alphabetical order, within sections.

The format and numbering of the 15th WHO Model List of Essential Medicines have been retained but, as indicated in the text, some sections have been deleted because they contain medicines that are not relevant for children.

In the List of Essential Medicines for Children, two additional symbols are used.

[a] indicates that there is an age restriction on use of the medicines; the details for each medicine are in Table 1.

R indicates that the Subcommittee has endorsed the medicine as essential but has requested a review of the efficacy and safety to confirm this decision, or to expand use to additional age groups.

The listing of a medicine on the Essential Medicines List carries no assurance as to pharmaceutical quality of an individual product. It is the responsibility of each local regulatory authority to ensure that each brand is of appropriate pharmaceutical quality (including stability) and that, when relevant, different brands are interchangeable.

Dosage forms of medicines are listed in alphabetical order and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

Entries of the type *oral liquid* are intended to permit any solution, suspension or other form of liquid. Granules or powder for reconstitution as an oral liquid may substitute for oral liquids, and typically carry benefits in the form of better stability and lower transport costs. If more than one type of oral liquid is available on the same market (e.g. solution, suspension, granules or powder for reconstitution), they may be interchanged and in such cases should be bioequivalent. It is preferable that oral liquids do not contain sugar and that solutions for children do not contain alcohol.

Entries of the type *tablet* are intended to allow various forms of immediate-release tablet such as scored, uncoated, film-coated, crushable, chewable, dispersible etc. Enteric coating, on the other hand, modifies drug release, and enteric-coated products are a modified-release dosage form. Crushable, chewable and dispersible tablets may be easier to administer to paediatric populations and to the elderly.

1. Anaesthetics

1.1 General anaesthetics and oxygen

☐ halothane R	Inhalation. R Review for alternative inhalational agents.
ketamine	Injection: 50 mg (as hydrochloride)/ml in 10-ml vial.
nitrous oxide	Inhalation.
oxygen	Inhalation (medicinal gas).
thiopental	Powder for injection: 0.5 g; 1.0 g (sodium salt) in ampoule.

1.2 Local anaesthetics

☐ bupivacaine	Injection: 0.25%; 0.5% (hydrochloride) in vial. Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.
☐ lidocaine	Injection: 1%; 2% (hydrochloride) in vial. Injection for spinal anaesthesia: 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution. Topical forms: 2% to 4% (hydrochloride).
lidocaine + epinephrine (adrenaline)	Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000. Injection: 1%; 2% (hydrochloride) + epinephrine 1:200 000 in vial.

1.3 Preoperative medication and sedation for short-term procedures

atropine R	Injection: 1 mg (sulfate) in 1-ml ampoule. R Relevance to current clinical practice?
☐ diazepam R	Injection: 5 mg/ml in 2-ml ampoule. Tablet: 5 mg. R Alternatives such as midazolam preferable?
morphine R	Injection: 10 mg (sulfate or hydrochloride) in 1-ml ampoule. R Need for review for the next meeting.

2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDs)

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

ibuprofen a R	Tablet: 200 mg; 400 mg. a >3 months. R Use in children, focusing on comparative analgesic efficacy and safety, include role of injection form in patent ductus arteriosus.

2. Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDs) *(continued)*

paracetamol*	Oral liquid: 125 mg/5 ml. Suppository: 100 mg. Tablet: 100 mg to 500 mg. * Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.
Complementary List	
*acetylsalicylic acid**	Suppository: *50 mg to 150 mg.* Tablet: *100 mg to 500 mg.* * *For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*

2.2 Opioid analgesics

codeine	Tablet: 15 mg (phosphate).
morphine	Injection: 10 mg (morphine hydrochloride or morphine sulfate) in 1-ml ampoule. Oral liquid: 10 mg (morphine hydrochloride or morphine sulfate)/5 ml. Tablet: 10 mg (morphine sulfate). Tablet (prolonged release): 10 mg; 30 mg; 60 mg (morphine sulfate).

~~2.3 Medicines used to treat gout~~

2.4 Disease modifying agents used in rheumatoid disorders (DMARDs) R

R The Subcommittee noted that there is a need for medicines for the treatment of juvenile arthritis but did not endorse any of the currently listed medicines at this time, requesting a review of this section.

3. Antiallergics and medicines used in anaphylaxis

☐ chlorphenamine a R	Injection: 10 mg (hydrogen maleate) in 1-ml ampoule. Oral liquid: 2 mg/5 ml. Tablet: 4 mg (hydrogen maleate). a >1 year. R Review of diphenhydramine to assess comparative efficacy and safety with chlorphenamine as a possible preferable alternative.
dexamethasone	Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.
epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
hydrocortisone	Powder for injection: 100 mg (as sodium succinate) in vial.

3. Antiallergics and medicines used in anaphylaxis *(continued)*

☐ prednisolone	Oral liquid: 5mg/ml. Tablet: 5 mg; 25 mg.

4. Antidotes and other substances used in poisonings

4.1 Non-specific

charcoal, activated	Powder

4.2 Specific R

R The Subcommittee recommended that this section be reviewed for its next meeting.

acetylcysteine	Injection: 200 mg/ml in 10-ml ampoule.
atropine	Injection: 1 mg (sulfate) in 1-ml ampoule.
calcium gluconate	Injection: 100 mg/ml in 10-ml ampoule.
deferoxamine	Powder for injection: 500 mg (mesilate) in vial.
dimercaprol	Injection in oil: 50 mg/ml in 2-ml ampoule.
naloxone	Injection: 400 micrograms (hydrochloride) in 1-ml ampoule.
penicillamine R	Capsule or tablet: 250 mg. R Comparative effectiveness and safety versus sodium calcium edetate.
sodium calcium edetate R	Injection: 200 mg/ml in 5-ml ampoule. R Comparative effectiveness and safety versus penicillamine.

5. Anticonvulsants/antiepileptics

carbamazepine	Oral liquid: 100 mg/5 ml. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg.
☐ diazepam R	Injection: 5 mg/ml in 2-ml ampoule (intravenous or rectal). R Review of benzodiazepines as alternative to diazepam (specifically consider comparative efficacy and safety of lorazepam and midazolam in relation to diazepam).
phenobarbital	Injection: 200 mg/ml (phenobarbital sodium). Oral liquid: 15 mg/5 ml (phenobarbital) or 5 ml (phenobarbital sodium). Tablet: 15 mg to 100 mg (phenobarbital).

5. Anticonvulsants/antiepileptics *(continued)*

phenytoin	Capsule: 25 mg; 50 mg; 100 mg (sodium salt). Injection: 50 mg/ml in 5-ml vial (sodium salt). Oral liquid: 25 mg to 30 mg/5 ml.* Tablet: 25 mg; 50 mg; 100 mg (sodium salt). Tablet (chewable): 50 mg. * The presence of both 25 mg/5 ml and 30 mg/5 ml strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
valproic acid (sodium valproate)	Oral liquid: 200 mg/5 ml. Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg (sodium salt).
Complementary List	
ethosuximide	Capsule: *250 mg.* Oral liquid: *250 mg/5 ml.*

6. Anti-infective medicines

6.1 Anthelminthics R

R Review evidence of efficacy and safety of use of anthelminth/antifilarial/antischistosomal and antitrematode medicines in children below the specified age in current licences.

6.1.1 *Intestinal anthelminthics* R

albendazole	Tablet (chewable): 400 mg.
levamisole	Tablet: 50 mg; 150 mg (as hydrochloride).
☐ mebendazole	Tablet (chewable): 100 mg; 500 mg.
niclosamide*	Tablet (chewable): 500 mg. * Niclosamide is listed for use when praziquantel treatment fails.
praziquantel	Tablet: 150 mg; 600 mg.
pyrantel	Oral liquid: 50 mg (as embonate)/ml. Tablet (chewable): 250 mg (as embonate).

6.1.2 *Antifilarials* R

ivermectin	Tablet (scored): 3 mg; 6 mg.
Complementary List	
diethylcarbamazine	Tablet: *50 mg; 100 mg (dihydrogen citrate).*

6.1.3 *Antischistosomals and antitrematode medicine* R

praziquantel	Tablet: 600 mg.
triclabendazole	Tablet: 250 mg.
Complementary List	
*oxamniquine**	Capsule: *250 mg.* Oral liquid: *250 mg/5 ml.* * *Oxamniquine is listed for use when praziquantel treatment fails.*

6.2 Antibacterials

6.2.1 *Beta Lactam medicines*

amoxicillin	Capsule or tablet: 250 mg; 500 mg (anhydrous). Powder for oral liquid: 125 mg (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml.
amoxicillin + clavulanic acid	Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 ml AND 250 mg amoxicillin + 62.5 mg clavulanic acid/5 ml. Tablet: 500 mg + 125 mg.
ampicillin	Powder for injection: 500 mg; 1 g (as sodium salt) in vial.
benzathine benzylpenicillin	Powder for injection: 900 mg benzylpenicillin (=1.2 million IU) in 5-ml vial; 1.44 g benzylpenicillin (=2.4 million IU) in 5-ml vial.
benzylpenicillin	Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.
☐ cefazolin* a	Powder for injection: 1 g (as sodium salt) in vial. * For surgical prophylaxis. a >1 month.
☐ ceftriaxone R	Powder for injection: 250 mg, 1 g (as sodium salt) in vial. R Review for safety of use in neonates.
☐ cloxacillin	Capsule: 500 mg; 1 g (as sodium salt). Powder for injection: 500 mg (as sodium salt) in vial. Powder for oral liquid: 125 mg (as sodium salt)/5 ml.

6. Anti-infective medicines *(continued)*

phenoxymethylpenicillin	Powder for oral liquid: 250 mg (as potassium salt)/5 ml. Tablet: 250 mg (as potassium salt).
procaine benzylpenicillin **a** **R**	Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial. **a** Not in neonates />1 month. **R** Review use of procaine penicillin in neonates.
Complementary List	
ceftazidime **R**	Powder for injection: *250 mg (as pentahydrate) in vial.* **R** Review the use of ceftazidime (predominantly for pseudomonas infections) — are there preferred alternatives for use in children?
imipenem + cilastatin** **R**	Powder for injection: *250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial.* * *Only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multidrug-resistant infection.* **R** Review the use of meropenem and other penems as alternative to imipenem, specifically identifying agents useful in all age groups.
6.2.2 *Other antibacterials*	
azithromycin* **a**	Capsule: 250 mg or 500 mg. Oral liquid: 200 mg/5 ml. * Only listed for trachoma. **a** >6 months.
chloramphenicol	Capsule: 250 mg. Oily suspension for injection*: 0.5 g (as sodium succinate)/ml in 2-ml ampoule * Only for the presumptive treatment of epidemic meningitis in children older than 2 years. Oral liquid: 150 mg (as palmitate)/5 ml. Powder for injection: 1 g (sodium succinate) in vial.
ciprofloxacin* **R**	Tablet: 250 mg (as hydrochloride). * Only for treatment of Shigella infections. **R** Review of appropriate use of fluroquinolones in children.

6. Anti-infective medicines *(continued)*

doxycycline* R	Capsule or tablet: 100 mg (hydrochloride). * For the treatment of cholera. R Review comparative safety and efficacy of tetracyclines (are tetracyclines other than doxycycline appropriate for this indication and therefore a square box listing is appropriate?).
erythromycin R	Capsule or tablet: 250 mg (as stearate or ethyl succinate). Powder for injection: 500 mg (as lactobionate) in vial. Powder for oral liquid: 125 mg (as stearate or ethyl succinate). R Review macrolides used in children for specific indications and whether erythromycin is the appropriate listed medicine. Review to consider use in neonates (risk of pyloric stenosis with erythromycin), relative toxicity and dosing compared to other macrolides. Include consideration of use of other macrolides for rheumatic fever.
☐ gentamicin R	Injection: 10 mg; 40 mg (as sulfate)/ml in 2-ml vial. R Review of evidence on ototoxicity for the next meeting.
metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Tablet: 200 mg to 500 mg.
nitrofurantoin	Oral liquid: 25 mg/5 ml. Tablet: 100 mg.
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml and 10-ml ampoules. Oral liquid: 200 mg + 40 mg/5 ml. Tablet: 100 mg + 20 mg; 400 mg + 80 mg.
trimethoprim a	Oral liquid: 50 mg/5 ml. Tablet: 100 mg; 200 mg. a >6 months.
Complementary List	
clindamycin a	Capsule: *150 mg.* Injection: *150 mg (as phosphate)/ml.* Oral liquid: *75 mg/5 ml.* a >1 month.

sulfadiazine R	Injection: *250 mg (sodium salt) in 4-ml ampoule.* Tablet: *500 mg.* R Review on use of sulfadiazine in children — especially safety, efficacy and dosing in toxoplasmosis.
vancomycin	Powder for injection: *250 mg (as hydrochloride) in vial.*

6.2.3 *Antileprosy medicines*

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

clofazimine	Capsule: 50 mg; 100 mg.
dapsone	Tablet: 25 mg; 50 mg; 100 mg.
rifampicin	Capsule or tablet: 150 mg; 300 mg.

6.2.4 *Antituberculosis medicines* R

R The Subcommittee requested a review of medicines used for TB in children, including evidence regarding dose, and alternatives for streptomycin.

ethambutol	Oral liquid: 25 mg/ml. Tablet: 100 mg; 400 mg (hydrochloride).
isoniazid	Oral liquid: 50 mg/5 ml. Tablet: 100 mg; 300 mg. Tablet (scored): 50 mg.
pyrazinamide	Oral liquid: 30 mg/ml. Tablet: 400 mg. Tablet (dispersible): 150 mg. Tablet (scored): 150 mg.
rifampicin	Capsule or tablet: 150 mg; 300 mg. Oral liquid: 20 mg/ml.
rifampicin + isoniazid	Tablet: 60 mg + 30 mg. 60 mg + 60 mg **(For intermittent use three times weekly).**
rifampicin + isoniazid + pyrazinamide	Tablet: 60 mg + 30 mg + 150 mg.
streptomycin	Powder for injection: 1 g (as sulfate) in vial.

6. Anti-infective medicines *(continued)*

Complementary List

Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control. R

R The Subcommittee has included these in recognition of the need for medicines for MDR-TB in children, but has not reviewed evidence at this meeting and therefore the section should be reviewed for the next meeting.

amikacin	Powder for injection: *1000 mg in vial.*
capreomycin	Powder for injection: *1000 mg in vial.*
cycloserine	Capsule or tablet: *250 mg.*
ethionamide	Tablet: *125 mg; 250 mg.*
kanamycin	Powder for injection: *1000 mg in vial.*
*ofloxacin**	Tablet: *200 mg; 400 mg.* * *Levofloxacin may be an alternative based on availability and programme considerations.*
p-aminosalicylic acid	Granules: *4 g in sachet.* Tablet: *500 mg.*

6.3 Antifungal medicines

fluconazole	Capsule: 50 mg. Injection: 2 mg/ml in vial. Oral liquid: 50 mg/5 ml.
griseofulvin	Capsule or tablet: 125 mg; 250 mg. Oral liquid: 125 mg/5ml.
nystatin	Lozenge: 100 000 IU. Oral liquid: 50 mg/5 ml; 100 000 IU/ml. Tablet: 100 000 IU; 500 000 IU.

Complementary List

amphotericin B	Powder for injection: *50 mg in vial.*
flucytosine	Capsule: *250 mg.* Infusion: *2.5 g in 250 ml.*
potassium iodide	Saturated solution.

6.4 Antiviral medicines

6.4.1 *Antiherpes medicines*

aciclovir	Oral liquid: 200 mg/5 ml. Powder for injection: 250 mg (as sodium salt) in vial. Tablet: 200 mg.

6.4.2 *Antiretrovirals*

Based on current evidence and experience of use, medicines in the following three classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post exposure prophylaxis). The Subcommittee emphasizes the importance of using these products in accordance with global and national guidelines. The Subcommittee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms with assured pharmaceutical quality.

The Subcommittee notes that scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided adequate quality products are available.

6.4.2.1 Nucleoside/Nucleotide reverse transcriptase inhibitors

abacavir (ABC)	Oral liquid: 100 mg (as sulfate)/5 ml. Tablet: 300 mg (as sulfate)**.**
didanosine (ddI)	Buffered powder for oral liquid: 100 mg; 167 mg; 250 mg packets. Capsule (unbuffered enteric-coated): 125 mg; 200 mg; 250 mg; 400 mg. Tablet (buffered chewable, dispersible): 25 mg; 50 mg; 100 mg; 150 mg; 200 mg.
emtricitabine (FTC)* **a**	Capsule: 200 mg. Oral liquid: 10 mg/ml. * FTC is an acceptable alternative to 3TC, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals. **a**>3 months.
lamivudine (3TC)	Oral liquid: 50 mg/5 ml. Tablet: 150 mg.
stavudine (d4T)	Capsule: 15 mg; 20 mg; 30 mg. Powder for oral liquid: 5 mg/5 ml.
zidovudine (ZDV or AZT)	Capsule: 100 mg; 250 mg. Oral liquid: 50 mg/5 ml. Solution for IV infusion injection: 10 mg/ml in 20-ml vial. Tablet: 300 mg.

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

efavirenz (EFV or EFZ) **a**	Capsule: 50 mg; 100 mg; 200 mg. Oral liquid: 150 mg/5 ml. Tablet: 600 mg. **a**>3 years or >10 kg weight.

nevirapine (NVP)	Oral liquid: 50 mg/5 ml. Tablet: 200 mg.

6.4.2.3 Protease inhibitors

Selection of protease inhibitor(s) from the Model List will need to be determined by each country after consideration of international and national treatment guidelines and experience. Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right.
This section will be reviewed. It is expected that application for a heat-stable tablet formulation containing 200/50 mg lopinavir + ritonavir will be submitted for the next meeting.

lopinavir + ritonavir (LPV/r)	Capsule: 133.3 mg + 33.3 mg. Oral liquid: 400 mg + 100 mg/5 ml.
nelfinavir (NFV)	Oral powder: 50 mg/g. Tablet: 250 mg (as mesilate).
ritonavir	Oral liquid: 400 mg/5 ml. Oral solid dosage form: 100 mg.
saquinavir (SQV) [a]	Capsule: 200 mg. [a] >25 kg weight.

Fixed-dose combinations

stavudine + lamivudine + nevirapine	Tablet: 30 mg + 150 mg + 200 mg.
zidovudine + lamivudine	Tablet: 300 mg + 150 mg.
zidovudine + lamivudine + nevirapine	Tablet: 300 mg + 150 mg + 200 mg.

6.4.3 *Other antivirals*

ribavirin*	Injection for intravenous administration: 800 mg and 1000 mg in 10-ml phosphate buffer solution. Oral solid dosage forms: 200 mg; 400 mg; 600 mg. * *For the treatment of viral haemorrhagic fevers only.*

6.5 Antiprotozoal medicines

6.5.1 *Antiamoebic and antigiardiasis medicines*

diloxanide [a][R]	Tablet: 500 mg (furoate). [a] >25 kg weight. [R] Review of effectiveness and safety for amoebiasis, with emphasis on comparative efficacy, safety, and age limits compared with oral paromomycin.

6. Anti-infective medicines *(continued)*

☐ metronidazole	Injection: 500 mg in 100-ml vial. Oral liquid: 200 mg (as benzoate)/5 ml. Tablet: 200 mg to 500 mg.

6.5.2 *Antileishmaniasis medicines*

paromomycin	Solution for intramuscular injection: 750 mg of paromomycin base present as the sulfate.
sodium stibogluconate or meglumine antimoniate	Injection: 100 mg/ml, 1 vial = 30 ml or 30%, equivalent to approximately 8.1% antimony in 5-ml ampoule.

Complementary List

amphotericin B	Powder for injection: *50 mg in vial.*

6.5.3 *Antimalarial medicines*

6.5.3.1 For curative treatment

Medicines for the treatment of *P. falciparum* malaria cases should be used in combination. The list currently recommends combinations according to treatment guidelines. The Subcommittee recognizes that not all of these FDCs exist and encourages their development and rigorous testing. The Subcommittee also encourages development and testing of rectal dosage formulations.

amodiaquine*	Tablet: 153 mg or 200 mg (as hydrochloride). * To be used (a) in combination with artesunate 50 mg OR (b) may be used alone for the treatment of *P.vivax, P.ovale* and *P.malariae* infections.
artemether	Oily injection: 80 mg/ml in 1-ml ampoule. For use in the management of severe malaria.
artemether + lumefantrine*	Tablet: 20 mg + 120 mg. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
artesunate*	Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution. For use in the management of severe malaria. Rectal dosage form: 50 mg; 200 mg capsules (for pre-referral treatment of severe malaria only; patients should be taken to an appropriate health facility for follow-up care). Tablet: 50 mg. * To be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.

chloroquine*	Oral liquid: 50 mg (as phosphate or sulfate)/5 ml. Tablet: 100 mg; 150 mg (as phosphate or sulfate). * For use only in central American regions, for use for *P.vivax*.
doxycycline*	Capsule: 100 mg (as hydrochloride). Tablet (dispersible): 100 mg (as monohydrate). * For use only in combination with quinine.
mefloquine*	Tablet: 250 mg (as hydrochloride). * To be used in combination with artesunate 50 mg.
primaquine*	Tablet: 7.5 mg; 15 mg (as diphosphate). * Only for use to achieve radical cure of *P.vivax* and *P.ovale* infections, given for 14 days.
quinine*	Injection: 300 mg quinine hydrochloride/ml in 2-ml ampoule. Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate). * For use only in the management of severe malaria, and should be used in combination with doxycycline.
sulfadoxine + pyrimethamine*	Tablet: 500 mg + 25 mg. * Only in combination with artesunate 50 mg.

6.5.3.2 For prophylaxis

chloroquine*	Oral liquid: 50 mg (as phosphate or sulfate)/5 ml. Tablet: 150 mg (as phosphate or sulfate). * For use only in central American regions, for use for *P.vivax*.
doxycycline [a]	Capsule or tablet: 100 mg (as hydrochloride). [a]>8 years.
mefloquine [a]	Tablet: 250 mg (as hydrochloride). [a]>5 kg or >3 months.
proguanil*	Tablet: 100 mg (as hydrochloride). * For use only in combination with chloroquine.

6.5.4 *Anti-pneumocystosis and antitoxoplasmosis medicines*

pyrimethamine	Tablet: 25 mg.
sulfamethoxazole + trimethoprim	Injection: 80 mg + 16 mg/ml in 5-ml ampoule; 80 mg + 16 mg/ml in 10-ml ampoule. Oral liquid: 200 mg + 40 mg/5 ml. Tablet: 100 mg + 20 mg; 400 mg + 80 mg.

6. Anti-infective medicines *(continued)*

6.5.5 *Antitrypanosomal medicines* R

R The Subcommittee requested a review of evidence for effectiveness and safety for medicines for trypanosomiasis in children for the next meeting.

6.5.5.1 African trypanosomiasis

Medicines for the treatment of 1st stage African trypanosomiasis

pentamidine*	Powder for injection: 200 mg (pentamidine isetionate) in vial. * To be used for the treatment of *Trypanosoma brucei gambiense* infection.
suramin sodium*	Powder for injection: 1 g in vial. * To be used for the treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Medicines for the treatment of 2nd stage African trypanosomiasis

eflornithine	Injection: 200 mg (hydrochloride)/ml in 100-ml bottle.
melarsoprol	Injection: 3.6% solution, 5-ml ampoules (180 mg of active compound).

6.5.5.2 American trypanosomiasis

benznidazole	Tablet: 100 mg.
nifurtimox	Tablet: 30 mg; 120 mg; 250 mg.

7. Antimigraine medicines

7.1 For treatment of acute attack

ibuprofen	Tablet: 200 mg; 400 mg.
paracetamol	Syrup: 125 mg/5 ml. Tablet: 300 mg to 500 mg.

7.2 For prophylaxis

propranolol	Tablet: 20 mg; 40 mg (hydrochloride).

8. Antineoplastic, immunosuppressives and medicines used in palliative care R

R The Subcommittee noted that these immunosuppressives and cytotoxics are essential for children but requested that these medicines be reviewed for the next meeting.

8.1 Immunosuppressive medicines

Complementary List

azathioprine	Powder for injection: *100 mg (as sodium salt) in vial.* Tablet: *50 mg.*

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

ciclosporin	Capsule: *25 mg.* Concentrate for injection: *50 mg/ml in 1-ml ampoule for organ transplantation.*

8.2 Cytotoxic medicines

Complementary List

allopurinol	Tablet: *100 mg to 300 mg.*
asparaginase	Powder for injection: *10 000 IU in vial.*
bleomycin	Powder for injection: *15 mg (as sulfate) in vial.*
calcium folinate	Injection: *3 mg/ml in 10-ml ampoule.* Tablet: *15 mg.*
chlorambucil	Tablet: *2 mg.*
cisplatin	Powder for injection: *10 mg; 50 mg in vial.*
cyclophosphamide	Powder for injection: *500 mg in vial.* Tablet: *25 mg.*
cytarabine	Powder for injection: *100 mg in vial.*
dacarbazine	Powder for injection: *100 mg in vial.*
dactinomycin	Powder for injection: *500 micrograms in vial.*
daunorubicin	Powder for injection: *50 mg (as hydrochloride).*
doxorubicin	Powder for injection: *10 mg; 50 mg (hydrochloride) in vial.*
etoposide	Capsule: *100 mg.* Injection: *20 mg/ml in 5-ml ampoule.*
fluorouracil	Injection: *50 mg/ml in 5-ml ampoule.*
mercaptopurine	Tablet: *50 mg.*
methotrexate	Powder for injection: *50 mg (as sodium salt) in vial.* Tablet: *2.5 mg (as sodium salt).*
procarbazine	Capsule: *50 mg (as hydrochloride).*
vinblastine	Powder for injection: *10 mg (sulfate) in vial.*
vincristine	Powder for injection: *1 mg; 5 mg (sulfate) in vial.*

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

8.3 Hormones and antihormones

Complementary List

dexamethasone	Injection: *4 mg dexamethasone phosphate (as disodium salt) in 1-ml ampoule.*
hydrocortisone	Powder for injection: *100 mg (as sodium succinate) in vial.*
*prednisolone**	Oral liquid: *5 mg/ml.* Tablet: *5 mg; 25 mg.* * *Prednisone should be considered equivalent to prednisolone.*

8.4 Medicines used in palliative care

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

~~9. Antiparkinsonism medicines~~

10. Medicines affecting the blood

10.1 Antianaemia medicines

The Subcommittee proposed a review of the evidence for appropriate dose combinations of iron and folic acid for children for consideration at its next meeting.

ferrous salt	Oral liquid: equivalent to 25 mg elemental iron/ml. Tablet: equivalent to 60 mg iron.
folic acid	Tablet: 1 mg; 5 mg.
hydroxocobalamin	Injection: 1 mg in 1-ml ampoule.

10.2 Medicines affecting coagulation

phytomenadione	Injection: 1 mg/ml; 10 mg/ml in 5-ml ampoule. Tablet: 10 mg.

Complementary List

heparin sodium	Injection: *1000 IU/ml; 5000 IU/ml; 20,000 IU/ml in 1-ml ampoule.*
protamine sulfate	Injection: *10 mg/ml in 5-ml ampoule.*
☐ *warfarin*	Tablet: *0.5 mg; 1.0 mg; 2.0 mg; 5.0 mg (sodium salt).*

11. Blood products and plasma substitutes

11.1 Plasma substitutes R

R The Subcommittee requested a review to determine whether these medicines are essential for children.

11.2 Plasma fractions for specific use

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

Complementary List

human normal immunoglobulin	Intramuscular administration: *16% protein solution.**
	Intravenous administration: *5%; 10% protein solution.***
	Subcutaneous administration: *15%; 16% protein solution.**
	** Indicated for primary immune deficiency.*
	*** Indicated for primary immune deficiency and Kawasaki disease.*
☐ *factor VIII concentrate*	Dried.
☐ *factor IX complex (coagulation factors, II, VII, IX, X) concentrate*	Dried.

12. Cardiovascular medicines

~~12.1 Antianginal medicines~~

12.2 Antiarrhythmic medicines R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

12.3 Antihypertensive medicines R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

12.4 Medicines used in heart failure R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section for the next meeting.

digoxin	Injection: 250 micrograms/ml in 2-ml ampoule.
	Oral liquid: 50 micrograms/ml.
	Tablet: 62.5 micrograms; 250 micrograms.
furosemide	Injection: 10 mg/ml in 2-ml ampoule.
	Oral liquid: 20 mg/5 ml.
	Tablet: 40 mg.

Complementary List

dopamine R	Injection: *40 mg (hydrochloride) in 5-ml vial.*
	R Review of safety and efficacy and place in therapy of dopamine in children.

12. Cardiovascular medicines *(continued)*

12.5 Antithrombotic medicines R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

12.6 Lipid-lowering agents R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

13. Dermatological medicines (topical) R

R The Subcommittee noted the need for a review of this section with alternative possible additions to the list.

13.1 Antifungal medicines

benzoic acid + salicylic acid	Ointment or cream: 6% + 3%.
☐ miconazole	Ointment or cream: 2% (nitrate).
Complementary List	
selenium sulfide	Detergent-based suspension: *2%.*

13.2 Anti-infective medicines

☐ methylrosanilinium chloride (gentian violet) R	Aqueous solution: 0.5%. Tincture: 0.5%. R Review of new evidence from ongoing trials.
neomycin sulfate + ☐ bacitracin	Ointment: 5 mg neomycin sulfate + 250 IU bacitracin zinc/g.
potassium permanganate	Aqueous solution: 1:10 000.
silver sulfadiazine [a]	Cream: 1%, in 500-g container. [a] >2 months.

13.3 Anti-inflammatory and antipruritic medicines

☐ betamethasone [a]	Cream or ointment: 0.1% (as valerate). [a] Hydrocortisone preferred in neonates.
calamine lotion	Lotion.
hydrocortisone	Cream or ointment: 1% (acetate).

13.4 Astringent medicines R

R The Subcommittee requested a review to determine whether these medicines are essential for children.

13.5 Medicines affecting skin differentiation and proliferation

benzoyl peroxide	Cream or lotion: 5%.
coal tar	Solution: 5%.
dithranol	Ointment: 0.1% to 2.0%.

13. Dermatological medicines (topical) R *(continued)*

☐ podophyllum resin	Solution: 10% to 25%.
salicylic acid	Solution: 5%.
urea	Cream or ointment: 10%.

13.6 Scabicides and pediculicides

☐ benzyl benzoate a R	Lotion: 25%. a >2 years. R Review of alternatives to benzyl benzoate for use in younger children (possible role for sulphur-based preparations in younger children).
permethrin	Cream: 5%. Lotion: 1%.

14. Diagnostic agents

14.1 Ophthalmic medicines

fluorescein	Eye drops: 1% (sodium salt).
☐ tropicamide	Eye drops: 0.5%.

14.2 Radiocontrast media R

R The Subcommittee requested a review of possible alternative contrast agents for use in children.

Complementary List

barium sulfate	Aqueous suspension.

15. Disinfectants and antiseptics

15.1 Antiseptics

☐ chlorhexidine	Solution: 5% (digluconate) for dilution.
☐ ethanol	Solution: 70% (denatured).
☐ polyvidone iodine	Solution: 10%.

15.2 Disinfectants

☐ chlorine base compound	Powder: (0.1% available chlorine) for solution.
☐ chloroxylenol	Solution: 4.8%.
glutaral	Solution: 2%.

16. Diuretics

furosemide	Injection: 10 mg/ml in 2-ml ampoule. Oral liquid: 20 mg/5 ml. Tablet: 10 mg; 20 mg; 40 mg.

16. Diuretics *(continued)*

Complementary List

☐ *hydrochlorothiazide*	Tablet (scored): *25 mg*.
mannitol R	Injectable solution: *10%; 20%*. R Review of comparative efficacy, safety and place in therapy of mannitol in children.
spironolactone R	Oral liquid: *1 to 20 mg/ml*. Tablet: *25 mg*. R Review of comparative efficacy, safety and place in therapy of spironolactone in children.

17. Gastrointestinal medicines

17.1 Antacids and other antiulcer medicines

aluminium hydroxide	Oral liquid: 320 mg/5 ml. Tablet: 500 mg.
magnesium hydroxide	Oral liquid: equivalent to 550 mg magnesium oxide/10 ml.
☐ ranitidine	Injection: 25 mg/ml in 2-ml ampoule. Oral liquid: 75 mg/5 ml. Tablet: 150 mg (as hydrochloride).

17.2 Antiemetic medicines

metoclopramide a	Injection: 5 mg (hydrochloride)/ml in 2-ml ampoule. Oral liquid: 5 mg/5 ml. Tablet: 10 mg (hydrochloride). a Not in neonates.
promethazine a	Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule. Oral liquid: 5 mg (hydrochloride)/5 ml. Tablet: 10 mg; 25 mg (hydrochloride). a >2 years.

~~**17.3 Anti-inflammatory medicines**~~

17.4 Laxatives R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

17. Gastrointestinal medicines *(continued)*

17.5 Medicines used in diarrhoea

17.5.1 *Oral rehydration*

oral rehydration salts	glucose: 75 mEq sodium: 75 mEq or mmol/l chloride: 65 mEq or mmol/l potassium: 20 mEq or mmol/l citrate: 10 mmol/l osmolarity: 245 mOsm/l glucose: 13.5 g/l sodium chloride: 2.6 g/l potassium chloride: 1.5 g/l trisodium citrate dihydrate+: 2.9 g/l + trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

17.5.2 *Medicines for diarrhoea in children*

zinc sulfate* R	Oral liquid: in 10 mg per unit dosage forms. Tablet: in 10 mg per unit dosage forms. * In acute diarrhoea zinc sulfate should be used as an adjunct to oral rehydration salts. R Review of availability of appropriate dosage forms.

~~17.5.3 *Antidiarrhoeal (symptomatic) medicines in adults*~~

18. Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes R

R The Subcommittee noted the need for adrenal hormones and requested that appropriate products be reviewed for possible inclusion.

~~**18.2 Androgens**~~

~~**18.3 Contraceptives**~~

~~18.3.1 *Oral hormonal contraceptives*~~

~~18.3.2 *Injectable hormonal contraceptives*~~

~~18.3.3 *Intrauterine devices*~~

~~18.3.4 *Barrier methods*~~

~~18.3.5 *Implantable contraceptives*~~

~~**18.4 Estrogens**~~

18.5 Insulins and other antidiabetic agents

insulin injection (soluble)	Injection: 40 IU/ml in 10-ml vial; 100 IU/ml in 10-ml vial.

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

intermediate-acting insulin	Injection: 40 IU/ml in 10-ml vial; 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin).
Complementary List	
metformin R	Tablet: *500 mg (hydrochloride).* R Review of public health relevance of this medicine in children.

~~**18.6 Ovulation inducers**~~

~~**18.7 Progestogens**~~

18.8 Thyroid hormones and antithyroid medicines

levothyroxine	Tablet: 25 micrograms; 50 micrograms; 100 micrograms (sodium salt).
Complementary List	
Lugol's solution	Oral liquid: *about 130 mg total iodine/ml.*
potassium iodide	Tablet: *60 mg.*
propylthiouracil R	Tablet: *50 mg.* R Review of use of propylthiouracil in children and appropriateness of carbimazole as an alternative.

19. Immunologicals

19.1 Diagnostic agents

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

tuberculin, purified protein derivative (PPD)	Injection.

19.2 Sera and immunoglobulins

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

antitetanus immunoglobulin (human)	Injection: 500 IU in vial.
antivenom immunoglobulin*	Injection. * Exact type to be defined locally.
diphtheria antitoxin	Injection: 10 000 IU; 20 000 IU in vial.
☐ rabies immunoglobulin	Injection: 150 IU/ml in vial.

19. Immunologicals *(continued)*

19.3 Vaccines

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

The Subcommittee noted the need for vaccines used in children to be polyvalent.

BCG vaccine

cholera vaccine

diphtheria vaccine

Haemophilus influenzae type b vaccine

hepatitis A vaccine

hepatitis B vaccine

influenza vaccine

Japanese encephalitis vaccine

measles vaccine

meningococcal meningitis vaccine

mumps vaccine

pertussis vaccine

pneumococcal vaccine

poliomyelitis vaccine

rabies vaccine

rotavirus vaccine

rubella vaccine

tetanus vaccine

typhoid vaccine

varicella vaccine

yellow fever vaccine

20. Muscle relaxants (peripherally-acting) and cholinesterase inhibitors R

R The Subcommittee recommended a review of the alternatives available for use in children.

neostigmine	Injection: 500 micrograms in 1-ml ampoule; 2.5 mg (metilsulfate) in 1-ml ampoule. Tablet: 15 mg (bromide).

20. Muscle relaxants (peripherally-acting) and cholinesterase inhibitors R *(continued)*

suxamethonium	Injection: 50 mg (chloride)/ml in 2-ml ampoule. Powder for injection: (chloride), in vial.
☐ vecuronium	Powder for injection: 10 mg (bromide) in vial.
Complementary List	
pyridostigmine	Injection: *1 mg in 1-ml ampoule.* Tablet: *60 mg (bromide).*

21. Ophthalmological preparations R

R The Subcommittee requested a review of newer medicines for potential additions to this list.

21.1 Anti-infective agents

aciclovir	Ointment: 3% W/W.
☐ gentamicin	Solution (eye drops): 0.3% (sulfate).
☐ tetracycline	Eye ointment: 1% (hydrochloride).

21.2 Anti-inflammatory agents

☐ prednisolone	Solution (eye drops): 0.5% (sodium phosphate).

21.3 Local anaesthetics

☐ tetracaine a	Solution (eye drops): 0.5% (hydrochloride). a Not in preterm neonates.

~~21.4 Miotics and antiglaucoma medicines~~

21.5 Mydriatics

atropine* a	Solution (eye drops): 0.1%; 0.5%; 1% (sulfate). * OR homatropine or cyclopentolate. a >3 months.
Complementary List	
epinephrine (adrenaline) R	Solution (eye drops): *2% (as hydrochloride).* R Review of anti-infective eye drops, identifying which are most appropriate for use in children.

~~22. Oxytocics and antioxytocics~~

~~22.1 Oxytocics~~

~~22.2 Antioxytocics (tocolytics)~~

23. Peritoneal dialysis solution

Complementary List

intraperitoneal dialysis solution (of appropriate composition)	Parenteral solution.

24. Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders R

R The Subcommittee requested a review of appropriate antipsychotics for use in children.

chlorpromazine	Injection: 25 mg (hydrochloride)/ml in 2-ml ampoule. Oral liquid: 25 mg (hydrochloride)/5 ml. Tablet: 10 mg; 25 mg; 50 mg; 100 mg (hydrochloride).
haloperidol	Injection: 5 mg in 1-ml ampoule. Oral liquid: 2 mg/ml. Oral solid dosage form: 0.5 mg; 2.0 mg; 5.0 mg.

24.2 Medicines used in mood disorders

24.2.1 *Medicines used in depressive disorders*

Complementary List

fluoxetine a	Capsule or tablet: *20 mg (present as hydrochloride).* a>8 years.

24.2.2 *Medicines used in bipolar disorders* R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

24.3 Medicines used in generalized anxiety and sleep disorders R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

24.4 Medicines used for obsessive compulsive disorders and panic attacks R

R The Subcommittee noted the potential importance of these medicines in children but requested a review of the section before endorsing any medicine as essential.

24.5 Medicines used in substance dependence programmes R

R The Subcommittee noted the potential importance of these medicines, particularly in neonates, but requested an assessment of the evidence before endorsing any medicine as essential.

25. Medicines acting on the respiratory tract

25.1 Antiasthmatic medicines

☐ budesonide	Inhalation (aerosol): 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose.

25. Medicines acting on the respiratory tract *(continued)*

epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule.
☐ salbutamol	Injection: 50 micrograms (as sulfate)/ml in 5-ml ampoule. Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose. Oral liquid: 2 mg/5 ml. R Review of the place in therapy of oral salbutamol preparations in children, with particular emphasis on efficacy and safety in asthma and in the wheezy child with acute respiratory tract infection. Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml. Tablet: 2 mg; 4 mg (as sulfate). R As for oral liquid.

25.2 Other medicines acting on the respiratory tract

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

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

26.1 Oral

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

26.2 Parenteral

glucose	Injectable solution: 5%; 10% isotonic; 50% hypertonic.
glucose with sodium chloride	Injectable solution: 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl- 30 mmol/l); 5% glucose, 0.9% sodium chloride (equivalent to 150 mmol/l Na^+ and 150 mmol/l Cl-); 5% glucose, 0.45% sodium chloride (equivalent to 75 mmol/l Na^+ and 75 mmol/l Cl-).
potassium chloride	Solution: 11.2% in 20-ml ampoule (equivalent to K^+ 1.5 mmol/ml, Cl- 1.5 mmol/ml).
sodium chloride	Injectable solution: 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl- 154 mmol/l).

26. Solutions correcting water, electrolyte and acid-base disturbances *(continued)*

sodium hydrogen carbonate	Injectable solution: 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_{3-} 167 mmol/l). Solution: 8.4% in 10-ml ampoule (equivalent to Na^+ 1000 mmol/l, HCO_{3-} 1000 mmol/l).
☐ sodium lactate, compound solution	Injectable solution.

26.3 Miscellaneous

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

27. Vitamins and minerals R

R The Subcommittee noted the need for a review of this section of the list to meet public health needs in children.

ascorbic acid	Tablet: 50 mg.
cholecalciferol*	Capsule or tablet: 400 IU; 1000 IU. Oral liquid: 400 IU/ml. * Ergocalciferol can be used as an alternative.
iodine	Capsule: 200 mg. Iodized oil: 1 ml (480 mg iodine); 0.5 ml (240 mg iodine) in ampoule (oral or injectable); 0.57 ml (308 mg iodine) in dispenser bottle.
pyridoxine	Tablet: 25 mg (hydrochloride).
retinol	Capsule: 50 000 IU; 100 000 IU; 200 000 IU (as palmitate). Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser. Tablet (sugar-coated): 10 000 IU (as palmitate). Water-miscible injection: 100 000 IU (as palmitate)in 2-ml ampoule.
riboflavin	Tablet: 5 mg.
sodium fluoride	In any appropriate topical formulation.
thiamine	Tablet: 50 mg (hydrochloride).
Complementary List	
calcium gluconate	Injection: *100 mg/ml in 10-ml ampoule.*

Table 1

Medicines with age restrictions

atropine	>3 months
azithromycin	>6 months
benzyl benzoate	>2 years
betamethasone topical preparations	Hydrocortisone preferred in neonates
cefazolin	>1 month
chlorphenamine	>1 year
clindamycin	>1 month
diloxanide	>25 kg weight
doxycycline	>8 years
efavirenz	>3 years or >10 kg weight
emtricitabine	>3 months
fluoxetine	>8 years
ibuprofen	>3 months
mefloquine	>5 kg or >3 months
metoclopramide	Not in neonates
procaine benzylpenicillin	Not in neonates />1 month
promethazine	>2 years
saquinavir	>25 kg weight
silver sulfadiazine	>2 months
tetracaine	Not in preterm neonates
trimethoprim	>6 months

Appendix 3

The Anatomical Therapeutic Chemical (ATC) classification system

ATC code	ATC group/medicine or item	Section
A	**ALIMENTARY TRACT AND METABOLISM**	
A02	**Drugs for acid related disorders**	
A02A	**Antacids**	
A02AA	*Magnesium compounds*	
A02AA04	magnesium hydroxide	17.1
A02AB	*Aluminium compounds*	
A02AB01	aluminium hydroxide	17.1
A02B	**Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)**	
A02BA	*H_2-receptor antagonists*	
A02BA02	ranitidine	17.1
A03	**Drugs for functional gastrointestinal disorders**	
A03B	**Belladonna and derivatives, plain**	
A03BA	*Belladonna alkaloids, tertiary amines*	
A03BA01	atropine	1.3; 4.2
A03F	**Propulsives**	
A03FA	*Propulsives*	
A03FA01	metoclopramide	17.2
A07	**Antidiarrheals, intestinal antiinflammatory/antiinfective agents**	
A07A	**Intestinal antiinfectives**	
A07AA	*Antibiotics*	
A07AA02	nystatin	6.3
A07AA06	paromomycin	6.5.2
A07B	**Intestinal adsorbents**	
A07BA	*Charcoal preparations*	
A07BA01	charcoal, activated*	4.1
A07C	**Electrolytes with carbohydrates**	
A07CA	*oral rehydration salts**	17.5.1; 26.1
A10	**Drugs used in diabetes**	
A10A	**Insulins and analogues**	
A10AB	*Insulins and analogues, fast-acting*	
A10AB	insulin injection (soluble)*	18.5
A10AC	*Insulins and analogues, intermediate-acting*	
A10AC	insulin, intermediate-acting*	18.5
A10B	**Oral blood glucose lowering drugs**	
A10BA	*Biguanides*	

ATC code	ATC group/medicine or item	Section
A10BA02	metformin	18.5
A11	**Vitamins**	
A11C	**Vitamin A and D, incl. combinations of the two**	
A11CA	*Vitamin A, plain*	
A11CA01	retinol	27
A11CC	*Vitamin D and analogues*	
A11CC01	ergocalciferol	27
A11D	**Vitamin B_1, plain and in combination with vitamin B_6 and B_{12}**	
A11DA	*Vitamin B_1, plain*	
A11DA01	thiamine	27
A11G	**Ascorbic acid (vitamin C), incl. combinations**	
A11GA	*Ascorbic acid (vitamin C), plain*	
A11GA01	ascorbic acid	27
A11H	**Other plain vitamin preparations**	
A11HA	*Other plain vitamin preparations*	
A11HA02	pyridoxine	27
A11HA04	riboflavin	27
A12	**Mineral supplements**	
A12A	**Calcium**	
A12AA	*Calcium*	
A12AA03	calcium gluconate	4.2; 27
A12AX	cholecalciferol	27
A12C	**Other mineral supplements**	
A12CB	*Zinc*	
A12CB01	zinc sulfate	17.5.2
A12CD	*Fluoride*	
A12CD01	sodium fluoride	27
A12CX	*Other mineral products*	
A12CX	iodine*	27
B	**BLOOD AND BLOOD FORMING ORGANS**	
B01	**Antithrombotic agents**	
B01A	**Antithrombotic agents**	
B01AA	*Vitamin K antagonists*	
B01AA03	warfarin	10.2
B01AB	*Heparin group*	
B01AB01	heparin sodium*	10.2
B02	**Antihemorrhagics**	
B02B	**Vitamin K and other hemostatics**	

ATC code	ATC group/medicine or item	Section
B02BA	*Vitamin K*	
B02BA01	phytomenadione	10.2
B02BD	*Blood coagulation factors*	
B02BD01	factor IX complex (coagulation factors II, VII, IX, X) concentrate*	11.2
B02BD02	factor VIII concentrate*	11.2
B03	**Antianemic preparations**	
B03A	ferrous salt*	10.1
B03B	**Vitamin B_{12} and folic acid**	
B03BA	Vitamin B_{12} (cyanocobalamin and analogues)	
B03BA03	hydroxocobalamin	10.1
B03BB	*Folic acid and derivatives*	
B03BB01	folic acid	10.1
B05	**Blood substitutes and perfusion solutions**	
B05B	**I.V. solutions**	
B05BB	*Solutions affecting the electrolyte balance*	
B05BB01	sodium lactate, compound solution*	26.2
B05BB02	glucose with sodium chloride*	26.2
B05BC	*Solutions producing osmotic diuresis*	
B05BC01	mannitol	16
B05D	**Peritoneal dialytics**	
B05DA	*intraperitoneal dialysis solution**	*23*
B05X	**I.V. solution additives**	
B05XA	*Electrolyte solutions*	
B05XA01	potassium chloride	26.1; 26.2
B05XA02	sodium hydrogen carbonate*	26.2
B05XA03	sodium chloride	26.2
C	**CARDIOVASCULAR SYSTEM**	
C01	**Cardiac therapy**	
C01A	**Cardiac glycosides**	
C01AA	*Digitalis glycosides*	
C01AA05	digoxin	12.4
C01C	**Cardiac stimulants excl. cardiac glycosides**	
C01CA	*Adrenergic and dopaminergic agents*	
C01CA04	dopamine	12.4
C01CA24	epinephrine (adrenaline)	3; 25.1
C03	**Diuretics**	
C03A	**Low-ceiling diuretics, thiazides**	
C03AA	*Thiazides, plain*	
C03AA03	hydrochlorothiazide	16
C03C	**High-ceiling diuretics**	

ATC code	ATC group/medicine or item	Section
C03CA	*Sulfonamides, plain*	
C03CA01	furosemide	12.4; 16
C03D	**Potassium-sparing agents**	
C03DA	*Aldosterone antagonists*	
C03DA01	spironolactone	16
C07	**Beta blocking agents**	
C07A	**Beta blocking agents**	
C07AA	*Beta blocking agents, non-selective*	
C07AA05	propranolol	7.2
D	**DERMATOLOGICALS**	
D01	**Antifungals for dermatological use**	
D01A	**Antifungals for topical use**	
D01AA	*Antibiotics*	
D01AA01	nystatin	6.3
D01AC	*Imidazole and triazole derivatives*	
D01AC02	miconazole	13.1
D01AE	*Other antifungals for topical use*	
D01AE02	methylrosanilinium chloride (gentian violet)*	13.2
D01AE12	salicylic acid	13.5
D01AE13	selenium sulfide	13.1
D01AE20	benzoic acid + salicylic acid*	13.1
D01B	**Antifungals for systemic use**	
D01BA	*Antifungals for systemic use*	
D01BA01	griseofulvin	6.3
D02	**Emollients and protectives**	
D02A	*Emollients and protectives*	
D02AB	*Zinc products*	
D02AB	calamine lotion*	13.3
D02AE	*Carbamide products*	
D02AE01	urea*	13.5
D05	**Antipsoriatics**	
D05A	**Antipsoriatics for topical use**	
D05AA	*Tars*	
D05AA	*coal tar**	*13.5*
D05AC	Antracen derivatives	
D05AC01	dithranol	13.5
D06	**Antibiotics and chemotherapeutics for dermatological use**	
D06A	**Antibiotics for topical use**	
D06AX	*Other antibiotics for topical use*	
D06AX04	neomycin + bacitracin*	13.2

ATC code	ATC group/medicine or item	Section
D06B	**Chemotherapeutics for topical use**	
D06BA	*Sulfonamides*	
D06BA01	silver sulfadiazine	13.2
D06BB	*Antivirals*	
D06BB04	podophyllum resin*	13.5
D07	**Corticosteroids, dermatological preparations**	
D07A	**Corticosteroids, plain**	
D07AA	Corticosteroids, weak (group I)	
D07AA02	hydrocortisone	13.3
D07AC	Corticosteroids, potent (group III)	
D07AC01	betamethasone	13.3
D08	**Antiseptics and disinfectants**	
D08A	**Antiseptics and disinfectants**	
D08AC	*Biguanides and amidines*	
D08AC02	chlorhexidine	15.1
D08AE	*Phenol and derivatives*	
D08AE05	chloroxylenol	15.2
D08AG	*Iodine products*	
D08AG02	polyvidone iodine	15.1
D08AX	*Other antiseptics and disinfectants*	
D08AX	chlorine base compound*	15.2
D08AX06	potassium permanganate	13.2
D08AX08	ethanol	15.1
D10	**Anti-acne preparations**	
D10A	**Anti-acne preparations for topical use**	
D10AE	*Peroxides*	
D10AE01	benzoyl peroxide	13.5
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	
G01	**Gynecological antiinfectives and antiseptics**	
G01A	**Antiinfectives and antiseptics, excl. combinations with corticosteroids**	
G01AA	*Antibiotics*	
G01AA01	nystatin	6.3
H	**SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS**	
H02	**Corticosteroids for systemic use**	
H02A	**Corticosteroids for systemic use, plain**	
H02AB	*Glucocorticoids*	
H02AB02	dexamethasone	3; 8.3

ATC code	ATC group/medicine or item	Section
H02AB06	prednisolone	3; 8.3
H02AB09	hydrocortisone	3; 8.3
H03	**Thyroid therapy**	
H03A	**Thyroid preparations**	
H03AA	*Thyroid hormones*	
H03AA01	levothyroxine*	18.8
H03B	**Antithyroid preparations**	
H03BA	*Thiouracils*	
H03BA02	propylthiouracil	18.8
H03C	**Iodine therapy**	
H03CA	*Iodine therapy*	
H03CA	potassium iodide*	6.3; 18.8
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	
J01	**Antibacterials for systemic use**	
J01A	**Tetracyclines**	
J01AA	*Tetracyclines*	
J01AA02	doxycycline	6.2.2; 6.5.3.1; 6.5.3.2
J01B	**Amphenicols**	
J01BA	*Amphenicols*	
J01BA01	chloramphenicol	6.2.2
J01C	**Beta-lactam antibacterials, penicillins**	
J01CA	*Penicillins with extended spectrum*	
J01CA01	ampicillin	6.2.1
J01CA04	amoxicillin	6.2.1
J01CE	*Beta-lactamase sensitive penicillins*	
J01CE01	benzylpenicillin	6.2.1
J01CE02	phenoxymethylpenicillin	6.2.1
J01CE08	benzathine benzylpenicillin	6.2.1
J01CE09	procaine benzylpenicillin*	6.2.1
J01CF	*Beta-lactamase resistant penicillins*	
J01CF02	cloxacillin	6.2.1
J01CR	*Combinations of penicillins, incl. beta-lactamase inhibitors*	
J01CR02	amoxicillin + clavulanic acid*	6.2.1
J01D	**Other beta-lactam antibacterials**	
J01DB	*First-generation cephalosporins*	
J01DB04	cefazolin	6.2.1
J01DD	*Third-generation cephalosporins*	
J01DD02	ceftazidime	6.2.1
J01DD04	ceftriaxone	6.2.1

ATC code	ATC group/medicine or item	Section
J01DH	*Carbapenems*	
J01DH51	imipenem + cilastatin*	6.2.1
J01E	**Sulfonamides and trimethoprim**	
J01EA	*Trimethoprim and derivatives*	
J01EA01	trimethoprim	6.2.2
J01EC	*Intermediate-acting sulfonamides*	
J01EC02	sulfadiazine	6.2.2
J01EE	*Combinations of sulfonamides and trimethoprim, incl. derivatives*	
J01EE01	sulfamethoxazole + trimethoprim	6.2.2; 6.5.4
J01F	**Macrolides, lincosamides and streptogramins**	
J01FA	*Macrolides*	
J01FA01	erythromycin	6.2.2
J01FA10	azithromycin	6.2.2
J01FF	*Lincosamides*	
J01FF01	clindamycin	6.2.2
J01G	**Aminoglycoside antibacterials**	
J01GA	*Streptomycins*	
J01GA01	streptomycin	6.2.4
J01GB	*Other aminoglycosides*	
J01GB03	gentamicin	6.2.2
J01GB04	kanamycin	6.2.4
J01GB06	amikacin	6.2.4
J01M	**Quinolone antibacterials**	
J01MA	*Fluoroquinolones*	
J01MA01	ofloxacin	6.2.4
J01MA02	ciprofloxacin	6.2.2
J01X	**Other antibacterials**	
J01XA	*Glycopeptide antibacterials*	
J01XA01	vancomycin	6.2.2
J01XD	*Imidazole derivatives*	
J01XD01	metronidazole	6.2.2
J01XE	*Nitrofuran derivatives*	
J01XE01	nitrofurantoin	6.2.2
J02	**Antimycotics for systemic use**	
J02A	**Antimycotics for systemic use**	
J02AA	*Antibiotics*	
J02AA01	amphotericin B	6.3; 6.5.2
J02AC	**Triazole derivatives**	
J02AC01	*fluconazole*	*6.3*

ATC code	ATC group/medicine or item	Section
J02AX	**Other antimycotics for systemic use**	
J02AX01	flucytosine	6.3
J04	**Antimycobacterials**	
J04A	**Drugs for treatment of tuberculosis**	
J04AA	*Aminosalicylic acid and derivatives*	
J04AA01	p-aminosalicylic acid*	6.2.4
J04AB	*Antibiotics*	
J04AB01	cycloserine	6.2.4
J04AB02	rifampicin	6.2.3; 6.2.4
J04AB30	capreomycin	6.2.4
J04AC	*Hydrazides*	
J04AC01	isoniazid	6.2.4
J04AD	*Thiocarbamide derivatives*	
J04AD03	ethionamide	6.2.4
J04AK	*Other drugs for treatment of tuberculosis*	
J04AK02	ethambutol	6.2.4
J04AM	*Combinations of drugs for treatment of tuberculosis*	
J04AM02	rifampicin + isoniazid*	6.2.4
J04AM03	isoniazid + ethambutol*	6.2.4
J04AM05	rifampicin + isoniazid + pyrazinamide*	6.2.4
J04B	**Drugs for treatment of lepra**	
J04BA	*Drugs for treatment of lepra*	
J04BA01	clofazimine	6.2.3
J04BA02	dapsone	6.2.3
J05	**Antivirals for systemic use**	
J05A	**Direct acting antivirals**	
J05AB	*Nucleosides and nucleotides excl. reverse transcriptase inhibitors*	
J05AB01	aciclovir	6.4.1
J05AB04	ribavirin	6.4.3
J05AE	*Protease inhibitors*	
J05AE01	saquinavir (SQV)	6.4.2.3
J05AE03	ritonavir (r)	6.4.2.3
J05AE04	nelfinavir (NFV)	6.4.2.3
J05AE30	lopinavir + ritonavir (LPV/r)*	6.4.2.3
J05AF	*Nucleoside reverse transcriptase inhibitors*	
J05AF01	zidovudine (ZDV or AZT)	6.4.2.1
J05AF02	didanosine (ddI)	6.4.2.1
J05AF04	stavudine (d4T)	6.4.2.1
J05AF05	lamivudine (3TC)	6.4.2.1
J05AF06	abacavir (ABC)	6.4.2.1
J05AF09	emtricitabine	6.4.2.1

ATC code	ATC group/medicine or item	Section
J05AG	*Non-nucleoside reverse transcriptase inhibitors*	
J05AG01	nevirapine (NVP)	6.4.2.2
J05AG03	efavirenz (EFV or EFZ)	6.4.2.2
J05AR01	zidovudine (ZDV or AZT) + lamivudine	6.4.2.3
J05AR05	zidovudine + lamivudine + nevirapine	6.4.2.3
	stavudine + lamivudine + nevirapine	6.4.2.3
J06	**Immune sera and immunoglobulins**	
J06A	**Immune sera**	
J06AA	*Immune sera*	
J06AA01	diphtheria antitoxin	19.2
J06AA03	antivenom immunoglobulin*	19.2
J06B	**Immunoglobulins**	
J06BB	*Specific immunoglobulins*	
J06BB02	antitetanus immunoglobulin (human)	19.2
J06BB05	rabies immunoglobulin	19.2
J07	**Vaccines**	
J07A	**Bacterial vaccines**	
J07AE	*Cholera vaccines*	
J07AE	cholera vaccine	19.3
J07AH	*Meningococcal vaccines*	
J07AH	meningococcal meningitis vaccine*	19.3
J07AJ	*Pertussis vaccines*	
J07AJ51	diphtheria-pertussis-tetanus vaccine*	19.3
J07AM	*Tetanus vaccines*	
J07AM51	diphtheria-tetanus vaccine*	19.3
J07AN	*Tuberculosis vaccines*	
J07AN01	BCG vaccine*	19.3
J07AP	*Typhoid vaccines*	
J07AP	typhoid vaccine	19.3
J07B	**Viral vaccines**	
J07BB	*Influenza vaccines*	
J07BB	influenza vaccine	19.3
J07BC	*Hepatitis vaccines*	
J07BC01	hepatitis B vaccine	19.3
J07BD	*Measles vaccine**	
J07BF	*poliomyelitis vaccine*	19.3
J07BG	*rabies vaccine*	19.3

ATC code	ATC group/medicine or item	Section
J07BJ	*rubella vaccine*	19.3
J07BL	*yellow fever vaccine*	19.3
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	
L01	**Antineoplastic agents**	
L01A	**Alkylating agents**	
L01AA	*Nitrogen mustard analogues*	
L01AA01	cyclophosphamide	8.2
L01AA02	chlorambucil	8.2
L01AX	*Other alkylating agents*	
L01AX04	dacarbazine	8.2
L01B	**Antimetabolites**	
L01BA	*Folic acid analogues*	
L01BA01	methotrexate	8.2
L01BB	*Purine analogues*	
L01BB02	mercaptopurine	8.2
L01BC	*Pyrimidine analogues*	
L01BC01	cytarabine	8.2
L01BC02	fluorouracil	8.2; 13.5
L01C	**Plant alkaloids and other natural products**	
L01CA	*Vinca alkaloids and analogues*	
L01CA01	vinblastine	8.2
L01CA02	vincristine	8.2
L01CB	*Podophyllotoxin derivatives*	
L01CB01	etoposide	8.2
L01D	**Cytotoxic antibiotics and related substances**	
L01DA	*Actinomycines*	
L01DA01	dactinomycin	8.2
L01DB	*Anthracyclines and related substances*	
L01DB01	doxorubicin	8.2
L01DB02	daunorubicin	8.2
L01DC	*Other cytotoxic antibiotics*	
L01DC01	bleomycin	8.2
L01X	**Other antineoplastic agents**	
L01XA	*Platinum compounds*	
L01XA01	cisplatin	8.2
L01XB	*Methylhydrazines*	
L01XB01	procarbazine	8.2
L01XX	*Other antineoplastic agents*	

ATC code	ATC group/medicine or item	Section
L01XX02	asparaginase	8.2
L04	**Immunosuppressive agents**	
L04A	**Immunosuppressive agents**	
L04AA	*Selective immunosuppressive agents*	
L04AA01	ciclosporin	8.1
L04AX	*Other immunosuppressive agents*	
L04AX01	azathioprine	8.1
M	**MUSCULO-SKELETAL SYSTEM**	
M01	**Antiinflammatory and antirheumatic products**	
M01A	**Antiinflammatory and antirheumatic products, non-steroids**	
M01AE	*Propionic acid derivatives*	
M01AE01	ibuprofen	2.1; 7.1
M01C	**Specific antirheumatic agents**	
M01CC	*Penicillamine and similar agents*	
M01CC01	penicillamine	4.2
M03AB	*Choline derivatives*	
M03AB01	suxamethonium	20
M03AC	*Other quaternary ammonium compounds*	
M03AC03	vecuronium	20
M04	**Antigout preparations**	
M04A	**Antigout preparations**	
M04AA	*Preparations inhibiting uric acid production*	
M04AA01	allopurinol	8.2
N	**NERVOUS SYSTEM**	
N01	**Anesthetics**	
N01A	**Anesthetics, general**	
N01AB	*Halogenated hydrocarbons*	
N01AB01	halothane	1.1
N01AF	*Barbiturates, plain*	
N01AF03	thiopental	1.1
N01AX	*Other general anesthetics*	
N01AX03	ketamine	1.1
N01AX13	nitrous oxide	1.1
N01B	**Anesthetics, local**	
N01BB	*Amides*	
N01BB01	bupivacaine	1.2
N01BB02	lidocaine	1.2
N01BB52	lidocaine + epinephrine (adrenaline)*	1.2

ATC code	ATC group/medicine or item	Section
N02	**Analgesics**	
N02A	**Opioids**	
N02AA	*Natural opium alkaloids*	
N02AA01	morphine	1.3; 2.2
N02B	**Other analgesics and antipyretics**	
N02BA	*Salicylic acid and derivatives*	
N02BA01	acetylsalicylic acid	2.1
N02BE	Anilides	
N02BE01	paracetamol	2.1; 7.1
N03	**Antiepileptics**	
N03A	**Antiepileptics**	
N03AA	*Barbiturates and derivatives*	
N03AA02	phenobarbital	5
N03AB	*Hydantoin derivatives*	
N03AB02	phenytoin	5
N03AD	*Succinimide derivatives*	
N03AD01	ethosuximide	5
N03AF	*Carboxamide derivatives*	
N03AF01	carbamazepine	5
N03AG	*Fatty acid derivatives*	
N03AG01	valproic acid	5
N05	**Psycholeptics**	
N05A	**Antipsychotics**	
N05AA	*Phenothiazines with aliphatic side-chain*	
N05AA01	chlorpromazine	24.1
N05AD	**Butyrophenone derivatives**	
N05AD01	haloperidol	24.1
N05B	**Anxiolytics**	
N05BA	*Benzodiazepine derivatives*	
N05BA01	diazepam	1.3; 5
N06	**Psychoanaleptics**	
N06A	**Antidepressants**	
N06AB	*Selective serotonin reuptake inhibitors*	
N06AB03	fluoxetine	24.2.1
N06B	**Psychostimulants, agents used for ADHD and nootropics**	
N06BC	*Xanthine derivatives*	
N06BC01	caffeine citrate	25.2
N07	**Other nervous system drugs**	

ATC code	ATC group/medicine or item	Section
N07A	**Parasympathomimetics**	
N07AA	*Anticholinesterases*	
N07AA01	neostigmine	20
N07AA02	pyridostigmine	20
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS**	
P01	**Antiprotozoals**	
P01A	**Agents against amoebiasis and other protozoal diseases**	
P01AB	*Nitroimidazole derivatives*	
P01AB01	metronidazole	6.5.1
P01AC	*Dichloroacetamide derivatives*	
P01AC01	diloxanide	6.5.1
P01B	**Antimalarials**	
P01BA	*Aminoquinolines*	
P01BA01	chloroquine	6.5.3.1; 6.5.3.2
P01BA03	primaquine	6.5.3.1
P01BA06	amodiaquine	6.5.3.1
P01BB	*Biguanides*	
P01BB01	proguanil	6.5.3.2
P01BC	*Methanolquinolines*	
P01BC01	quinine	6.5.3.1
P01BC02	mefloquine	6.5.3.1; 6.5.3.2
P01BD	*Diaminopyrimidines*	
P01BD01	pyrimethamine	6.5.4
P01BD51	sulfadoxine + pyrimethamine*	6.5.3.1
P01BE	*Artemisinin and derivatives*	
P01BE02	artemether	6.5.3.1
P01BE03	artesunate	6.5.3.1
P01BE52	artemether + lumefantrine*	6.5.3.1
P01C	**Agents against leishmaniasis and trypanosomiasis**	
P01CA	*Nitroimidazole derivatives*	
P01CA02	benznidazole	6.5.5.2
P01CB	*Antimony compounds*	
P01CB01	meglumine antimoniate	6.5.2
P01CC	*Nitrofuran derivatives*	
P01CC01	nifurtimox	6.5.5.2
P01CD	*Arsenic compounds*	
P01CD01	melarsoprol	6.5.5.1
P01CX	*Other agents against leishmaniasis and trypanosomiasis*	

ATC code	ATC group/medicine or item	Section
P01CX01	pentamidine*	6.5.2; 6.5.4; 6.5.5.1
P01CX02	suramin sodium	6.1.2; 6.5.5.1
P01CX03	eflornithine	6.5.5.1
P02	**Anthelmintics**	
P02B	**Antitrematodals**	
P02BA	*Quinoline derivatives and related substances*	
P02BA01	praziquantel	6.1.1; 6.1.3
P02BA02	oxamniquine	6.1.3
P02BX	Other antitrematodal agents	
P02BX04	triclabendazole	6.1.3
P02C	**Antinematodal agents**	
P02CA	Benzimidazole derivatives	
P02CA01	mebendazole	6.1.1
P02CA03	albendazole	6.1.1
P02CB	Piperazine and derivatives	
P02CB02	diethylcarbamazine	6.1.2
P02CC	*Tetrahydropyrimidine derivatives*	
P02CC01	pyrantel	6.1.1
P02CE	*Imidazothiazole derivatives*	
P02CE01	levamisole	6.1.1
P02CF	*Avermectines*	
P02CF01	ivermectin	6.1.2
P02D	**Anticestodals**	
P02DA	*Salicylic acid derivatives*	
P02DA01	niclosamide	6.1.1
P03	**Ectoparasiticides, incl. scabicides, insecticides and repellents**	
P03A	**Ectoparasiticides, incl. scabicides**	
P03AC	*Pyrethrines, incl. synthetic compounds*	
P03AC04	permethrin	13.6
P03AX	*Other ectoparasiticides, incl. scabicides*	
P03AX01	benzyl benzoate	13.6
R	**RESPIRATORY SYSTEM**	
R03	**Drugs for obstructive airway diseases**	
R03A	*Adrenergics, inhalants*	
R03AC	*Selective beta-2-adrenoreceptor agonists*	
R03AC02	salbutamol	25.1

ATC code	ATC group/medicine or item	Section
R03C	**Adrenergics for systemic use**	
R03CA	*Alpha- and beta-adrenoreceptor agonists*	
R03CA02	ephedrine	1.2
R03CC	*Selective beta-2-adrenoreceptor agonists*	
R03CC02	salbutamol	25.1
R05	**Cough and cold preparations**	
R05D	**Cough suppressants, excl. combinations with expectorants**	
R05DA	*Opium alkaloids and derivatives*	
R05DA04	codeine	2.2
R06	**Antihistamines for systemic use**	
R06A	**Antihistamines for systemic use**	
R06AB	*Substituted alkylamines*	
R06AB04	chlorphenamine	3
R06AD	*Phenothiazine derivatives*	
R06AD02	promethazine	17.2
S	**SENSORY ORGANS**	
S01	**Ophthalmologicals**	
S01A	**Antiinfectives**	
S01AA	*Antibiotics*	
S01AA09	tetracycline	21.1
S01AA11	gentamicin	21.1
S01AD	*Antivirals*	
S01AD03	aciclovir	21.1
S01B	**Antiinflammatory agents**	
S01BA	*Corticosteroids, plain*	
S01BA04	prednisolone	21.2
S01E	**Antiglaucoma preparations and miotics**	
S01EA	*Sympathomimetics in glaucoma therapy*	
S01EA01	epinephrine	21.5
S01F	**Mydriatics and cycloplegics**	
S01FA	*Anticholinergics*	
S01FA01	atropine	21.5
S01FA06	tropicamide	14.1
S01H	**Local anesthetics**	
S01HA	*Local anesthetics*	
S01HA03	tetracaine	21.3

ATC code	ATC group/medicine or item	Section
S01J	**Diagnostic agents**	
S01JA	*Colouring agents*	
S01JA01	fluorescein	14.1
V	**VARIOUS**	
V03	**All other therapeutic products**	
V03A	**All other therapeutic products**	
V03AB	*Antidotes*	
V03AB03	sodium calcium edetate*	4.2
V03AB08	sodium nitrite	4.2
V03AB09	dimercaprol	4.2
V03AB14	protamine sulfate*	10.2
V03AB15	naloxone	4.2
V03AB23	acetylcysteine	4.2
V03AC	*Iron chelating agents*	
V03AC01	deferoxamine	4.2
V03AF	**Detoxifying agents for antineoplastic treatment**	
V03AF03	*calcium folinate*	*8.2*
V03AN	*Medical gases*	
V03AN	oxygen	1.1
V04	**Diagnostic agents**	
V04C	**Other diagnostic agents**	
V04CF	*Tuberculosis diagnostics*	
V04CF01	tuberculin, purified protein derivative (PPD)*	19.1
V07	**All other non-therapeutic products**	
V07A	**All other non-therapeutic products**	
V07AB	*Solvents and diluting agents, incl. irrigating solutions*	
V07AB	water for injection*	26.3
V07AV	**Technical disinfectants**	
V07AV	glutaral	15.2
V08	**Contrast media**	
V08B	**X-ray contrast media, non-iodinated**	
V08BA	*Barium sulfate containing X-ray contrast media*	
V08BA01	barium sulfate*	14.2

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

Appendix 4

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

ATC group/medicine or item	ATC code	SECTION
abacavir (ABC)	J05AF06	6.4.2.1
acetylcysteine	V03AB23	4.2
acetylsalicylic acid	N02BA01	2.1
aciclovir	J05AB01	6.4.1
aciclovir	S01AD03	21.1
albendazole	P02CA03	6.1.1
allopurinol	M04AA01	8.2
aluminium hydroxide	A02AB01	17.1
amikacin	J01GB06	6.2.4
amodiaquine	P01BA06	6.5.3.1
amoxicillin	J01CA04	6.2.1
amoxicillin + clavulanic acid*	J01CR02	6.2.1
amphotericin B	J02AA01	6.3; 6.5.2
ampicillin	J01CA01	6.2.1
antitetanus immunoglobulin (human)	J06BB02	19.2
antivenom immunoglobulin*	J06AA03	19.2
artemether	P01BE02	6.5.3.1
artemether + lumefantrine*	P01BE52	6.5.3.1
artesunate	P01BE03	6.5.3.1
ascorbic acid	A11GA01	27
asparaginase	L01XX02	8.2
atropine	A03BA01	1.3; 4.2
atropine	S01FA01	21.5
azathioprine	L04AX01	8.1
azithromycin	J01FA10	6.2.2
barium sulfate*	V08BA01	14.2
BCG vaccine*	J07AN01	19.3
benzathine benzylpenicillin	J01CE08	6.2.1
benznidazole	PO1CA02	6.5.5.2
benzoic acid + salicylic acid*	D01AE20	13.1

ATC group/medicine or item	ATC code	SECTION
benzoyl peroxide	D10AE01	13.5
benzyl benzoate	P03AX01	13.6
benzylpenicillin	J01CE01	6.2.1
betamethasone	D07AC01	13.3
bleomycin	L01DC01	8.2
budesonide	R03BA02	25.1
bupivacaine	N01BB01	1.2
caffeine citrate	N06BC01	25.2
calamine lotion*	D02AB	13.3
calcium folinate	V03AF03	8.2
calcium gluconate	A12AA03	4.2; 27
capreomycin	J04AB30	6.2.4
carbamazepine	N03AF01	5
cefazolin	J01DB04	6.2.1
ceftazidime	J01DD02	6.2.1
ceftriaxone	J01DD04	6.2.1
charcoal, activated*	A07BA01	4.1
chlorambucil	L01AA02	8.2
chloramphenicol	J01BA01	6.2.2
chlorhexidine	D08AC02	15.1
chlorine base compound*	D08AX	15.2
chloroquine	P01BA01	6.5.3.1; 6.5.3.2
chloroxylenol	D08AE05	15.2
chlorphenamine	R06AB04	3
chlorpromazine	N05AA01	24.1
cholecalciferol	A12AX	27
cholera vaccine	J07AE	19.3
ciclosporin	L04AA01	8.1
ciprofloxacin	J01MA02	6.2.2
cisplatin	L01XA01	8.2
clindamycin	J01FF01	6.2.2
clofazimine	J04BA01	6.2.3
cloxacillin	J01CF02	6.2.1
coal tar*	D05AA	13.5
codeine	R05DA04	2.2
cyclophosphamide	L01AA01	8.2

ATC group/medicine or item	ATC code	SECTION
cycloserine	J04AB01	6.2.4
cytarabine	L01BC01	8.2
dacarbazine	L01AX04	8.2
dactinomycin	L01DA01	8.2
dapsone	J04BA02	6.2.3
daunorubicin	L01DB02	8.2
deferoxamine	V03AC01	4.2
dexamethasone	H02AB02	3; 8.3
diazepam	N05BA01	1.3; 5
didanosine (ddI)	J05AF02	6.4.2.1
diethylcarbamazine	P02CB02	6.1.2
digoxin	C01AA05	12.4
diloxanide	P01AC01	6.5.1
dimercaprol	V03AB09	4.2
diphtheria antitoxin	J06AA01	19.2
diphtheria vaccine*	J07AF	19.3
dithranol	D05AC01	13.5
dopamine	C01CA04	12.4
doxorubicin	L01DB01	8.2
doxycycline	J01AA02	6.2.2; 6.5.3.1; 6.5.3.2
efavirenz (EFV or EFZ)	J05AG03	6.4.2.2
eflornithine	P01CX03	6.5.5.1
emtricitabine	J05AF09	6.4.2.1
ephedrine	R03CA02	1.2
epinephrine	S01EA01	21.5
epinephrine (adrenaline)	C01CA24	3; 25.1
erythromycin	J01FA01	6.2.2
ethambutol	J04AK02	6.2.4
ethanol	D08AX08	15.1
ethionamide	J04AD03	6.2.4
ethosuximide	N03AD01	5
etoposide	L01CB01	8.2
factor IX complex (coagulation factors II, VII, IX, X) concentrate*	B02BD01	11.2

ATC group/medicine or item	ATC code	SECTION
factor VIII concentrate*	B02BD02	11.2
ferrous salt*	B03A	10.1
fluconazole	J02AC01	6.3
flucytosine	J02AX01	6.3
fluorescein	S01JA01	14.1
fluorouracil	L01BC02	8.2; 13.5
fluoxetine	N06AB03	24.2.1
folic acid	B03BB01	10.1
furosemide	C03CA01	12.4; 16
gentamicin	J01GB03	6.2.2
gentamicin	S01AA11	21.1
glucose	B05CX01	26.2
glucose with sodium chloride*	B05BB02	26.2
glutaral	V07AV	15.2
griseofulvin	D01BA01	6.3
haemophilius influenzae type b vaccine	J07AG	19.3
haloperidol	N05AD01	24.1
halothane	N01AB01	1.1
heparin sodium*	B01AB01	10.2
hepatitis A vaccine	J07BC02	19.3
hepatitis B vaccine	J07BC01	19.3
hydrochlorothiazide	C03AA03	16
hydrocortisone	D07AA02	13.3
hydrocortisone	H02AB09	3; 8.3
hydroxocobalamin	B03BA03	10.1
ibuprofen	M01AE01	2.1; 7.1
imipenem + cilastatin*	J01DH51	6.2.1
immunoglobulins, normal human, for intravascular adm.	J06BA02	11.2
influenza vaccine	J07BB	19.3
insulin injection (soluble)*	A10AB	18.5
insulin, intermediate-acting*	A10AC	18.5
intraperitoneal dialysis solution*	B05DA	23
iodine*	A12CX	27
isoniazid	J04AC01	6.2.4

ATC group/medicine or item	ATC code	SECTION
ivermectin	P02CF01	6.1.2
Japanese encephalitis vaccine	J07BA02	19.3
kanamycin	J01GB04	6.2.4
ketamine	N01AX03	1.1
lamivudine (3TC)	J05AF05	6.4.2.1
levamisole	P02CE01	6.1.1
levothyroxine*	H03AA01	18.8
lidocaine	N01BB02	1.2
lidocaine + epinephrine (adrenaline)*	N01BB52	1.2
lopinavir + ritonavir (LPV/r)*	J05AE30	6.4.2.3
Lugol's solution	D08AG	18.8
magnesium hydroxide	A02AA04	17.1
mannitol	B05BC01	16
measles vaccine*	J07BD52	19.3
mebendazole	P02CA01	6.1.1
mefloquine	P01BC02	6.5.3.1; 6.5.3.2
meglumine antimoniate	P01CB01	6.5.2
melarsoprol	P01CD01	6.5.5.1
meningococcal meningitis vaccine*	J07AH	19.3.2
mercaptopurine	L01BB02	8.2
metformin	A10BA02	18.5
methotrexate	L01BA01	8.2
methylrosanilinium chloride (gentian violet)*	D01AE02	13.2
metoclopramide	A03FA01	17.2
metronidazole	J01XD01	6.2.2
metronidazole	P01AB01	6.5.1
miconazole	D01AC02	13.1
morphine	N02AA01	1.3; 2.2
mumps vaccine	J07BE01	19.3
naloxone	V03AB15	4.2
nelfinavir (NFV)	J05AE04	6.4.2.3
neomycin + bacitracin*	D06AX04	13.2

ATC group/medicine or item	ATC code	SECTION
neostigmine	N07AA01	20
nevirapine (NVP)	J05AG01	6.4.2.2
niclosamide	P02DA01	6.1.1
nifurtimox	P01CC01	6.5.5.2
nitrofurantoin	J01XE01	6.2.2
nitrous oxide	N01AX13	1.1
nystatin	A07AA02	6.3
nystatin	D01AA01	6.3
nystatin	G01AA01	6.3
ofloxacin	J01MA01	6.2.4
oral rehydration salts*	A07CA	17.5.1; 26.1
oxamniquine	P02BA02	6.1.3
oxygen	V03AN	1.1
p-aminosalicylic acid*	J04AA01	6.2.4
paracetamol	N02BE01	2.1; 7.1
paromomycin	A07AA06	6.5.2
penicillamine	M01CC01	4.2
pentamidine*	P01CX01	6.5.5.1
permethrin	P03AC04	13.6
pertussis vaccine	J07AJ	19.3
phenobarbital	N03AA02	5
phenoxymethylpenicillin	J01CE02	6.2.1
phenytoin	N03AB02	5
phytomenadione	B02BA01	10.2
pneumococcal vaccine	J07AL	19.3
podophyllum resin*	D06BB04	13.5
poliomyelitis vaccine	J07BF	19.3.1
polyvidone iodine	D08AG02	15.1
potassium chloride	B05XA01	26.1; 26.2
potassium iodide*	H03CA	6.3; 18.8
potassium permanganate	D08AX06	13.2
praziquantel	P02BA01	6.1.1; 6.1.3
prednisolone	H02AB06	3; 8.3
prednisolone	S01BA04	21.2
primaquine	P01BA03	6.5.3.1

ATC group/medicine or item	ATC code	SECTION
procaine benzylpenicillin*	J01CE09	6.2.1
procarbazine	L01XB01	8.2
proguanil	P01BB01	6.5.3.2
promethazine	R06AD02	17.2
propranolol	C07AA05	7.2
propylthiouracil	H03BA02	18.8
protamine sulfate*	V03AB14	10.2
pyrantel	P02CC01	6.1.1
pyrazinamide	J04AK01	6.2.4
pyridostigmine	N07AA02	20
pyridoxine	A11HA02	27
pyrimethamine	P01BD01	6.5.4
quinine	P01BC01	6.5.3.1
rabies immunoglobulin	J06BB05	19.2
rabies vaccine	J07BG	19.3
ranitidine	A02BA02	17.1
retinol	A11CA01	27
ribavirin	J05AB04	6.4.3
riboflavin	A11HA04	27
rifampicin	J04AB02	6.2.3; 6.2.4
rifampicin + isoniazid*	J04AM02	6.2.4
rifampicin + isoniazid + pyrazinamide*	J04AM05	6.2.4
ritonavir (r)	J05AE03	6.4.2.3
rotavirus vaccine	J07BH01	19.3
rubella vaccine	J07BJ	19.3
salbutamol	R03CC02	25.1
salicylic acid	D01AE12	13.5
saquinavir (SQV)	J05AE01	6.4.2.3
selenium sulfide	D01AE13	13.1
silver sulfadiazine	D06BA01	13.2
sodium calcium edetate*	V03AB03	4.2
sodium chloride	B05XA03	26.2
sodium fluoride	A12CD01	27
sodium hydrogen carbonate*	B05XA02	26.2

ATC group/medicine or item	ATC code	SECTION
sodium lactate, compound solution*	B05BB01	26.2
sodium stibogluconate	PB1CB02	6.5.2
spironolactone	C03DA01	16
stavudine (d4T)	J05AF04	6.4.2.1
stavudine + lamivudine + nevirapine		6.4.2.3
streptomycin	J01GA01	6.2.4
sulfadiazine	J01EC02	6.2.2
sulfadoxine + pyrimethamine*	P01BD51	6.5.3.1
sulfamethoxazole + trimethoprim	J01EE01	6.2.2; 6.5.4
suramin sodium	P01CX02	6.5.5.1
suxamethonium	M03AB01	20
tetanus vaccine	J07AM	19.3
tetracaine	S01HA03	21.3
tetracycline	S01AA09	21.1
thiamine	A11DA01	27
thiopental	N01AF03	1.1
triclabendazole	P02BX04	6.1.3
trimethoprim	J01EA01	6.2.2
tropicamide	S01FA06	14.1
tuberculin, purified protein derivative (PPD)*	V04CF01	19.1
typhoid vaccine	J07AP	19.3
urea*	D02AE01	13.5
valproic acid	N03AG01	5
vancomycin	J01XA01	6.2.2
varicella vaccine	J07BK01	19.3
vecuronium	M03AC03	20
vinblastine	L01CA01	8.2
vincristine	L01CA02	8.2
warfarin	B01AA03	10.2
water for injection*	V07AB	26.3
yellow fever vaccine	J07BL	19.3.2

ATC group/medicine or item	ATC code	SECTION
zidovudine (ZDV or AZT)	J05AF01	6.4.2.1
zidovudine (ZDV or AZT) + lamivudine	J05AR01	6.4.2.3
zidovudine + lamivudine + nevirapine	J05AR05	6.4.2.3
zinc sulfate	A12CB01	17.5.2

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

Appendix 5

Summary of reviews requested during the Subcommittee meeting

Section 1 Anaesthetics

1.1 Halothane listing with square box: review for alternative inhalational agents.

1.3 Retain morphine: problems with overdose, inappropriate dose in ampoule, need for appropriate alternative opioid.

1.3 Promethazine not endorsed: need to review for next meeting to assess relevance for Section (pre-operative medication and sedation for short-term procedures).

Section 2 Analgesics, antipyretics, NSAIDs, DMARDs

2.1 Review on ibuprofen use in children focusing on comparative analgesic efficacy and safety, include role of injection form in PDA.

2.1 Review of tramadol use in children.

2.4 DMARDs: review of importance of these medicines in children, age limits for use of specific agents, efficacy and safety of medicines and appropriate paediatric formulations.

Section 3 Antiallergics, medicines used in anaphylaxis

Review of diphenhydramine to assess comparative efficacy and safety with chlorphenamine; is this drug applicable to a broader age range of children than chorphenamine?

Review and preparation of application for a non-sedating antihistamine for use in children.

Section 4 Antidotes

Review of antidotes, specifically addressing lead poisoning and organophosphate poisoning in children. Consider the role of DMSA, pralidoxime (or other oximes for square box listing) in the review.

Section 5 Anticonvulsants/antiepileptics

Review of benzodiazepines as alternative to diazepam (specifically consider comparative efficacy and safety of lorazepam and midazolam and in relation to diazepam).

Review of newer agents (including lamotrigine) as anticonvulsants in children.

Review the evidence for intravenous sodium valproate for status epilepticus.

Section 6 Anti-infective agents

6.1 Review evidence of efficacy and safety of use of anthelminth/antifilarial/antischistosomal and antitrematode medicines in children below the licensing age limits.

6.2.1 Review use of procaine penicillin in neonates.

6.2.1 Review and preparation of application for inclusion of oral cephalosporin for use in children (indications include UTI, osteomyelitis).

6.2.1 Review the use of meropenem and other penems as alternative to imipenem, specifically identifying agents useful in all age groups. If appropriate, preparation of an application for inclusion of alternative for next meeting.

6.2.1 Review the use of ceftazidime (predominantly for Pseudomonas infections) — are there preferred alternatives for use in children?

6.2.2 Review macrolides used in children for specific indications and whether erythromycin is the appropriate listed medicine. Review to consider use in neonates (risk of pyloric stenosis with erythromycin), relative toxicity and dosing compared to other macrolides. Include consideration of use of other macrolides for rheumatic fever.

6.2.2. Review of the use of fluoroquinolones in children focusing on efficacy, safety and rational use of these agents in children.

6.2.2 Review comparative safety and efficacy of tetracyclines (context is endorsing 3-day treatment schedule for cholera in children — are tetracyclines other than doxycycline appropriate for this indication and therefore a square box listing appropriate).

6.2.2 Review on use of sulfadiazine in children — safety, efficacy and dosing in toxoplasmosis with a focus on licensing in children.

6.2.4 Review of drugs for second-line treatment of TB (MDR-TB) in children.

6.2.4 Review of efficacy, safety, place in therapy of rifabutin and rifapentin in management of TB with HIV co-infection in children.

6.5 Review of diloxanide for amoebiasis, with emphasis on comparative efficacy, safety, and age limits with oral paromomycin.

6.5 Review of efficacy and safety of pentamidine, suramin sodium, eflornithine, and melarsoprol for the treatment of African trypanosomiasis.

6.5 Review of efficacy and safety of benznidazole and nirfurtimox for the treatment of American trypanosomiasis.

Section 8 Antineoplastic, inmmunosuppressives and medicines used in palliative care

Review of key tumours and malignancies of childhood, focus on treatable conditions and identify medicines that are relevant and appropriate dose forms for children. Identified malignancies were acute lymphocytic leukaemia, Burkitt's lymphoma, Hodgkin's and non-Hodgkin's lymphoma, Wilms tumour, retinoblastoma and Kaposi's sarcoma.

Section 10 Medicines affecting the blood

10.1 Review of appropriate dose combinations of iron and folic acid for children.

Section 11 Blood products and plasma substitutes

11.1 Review of place in therapy of dextran 70 solution.

Section 12 Cardiovascular medicines

12.2 Review of medicines for arrhythmias in children.

12.3 Review of medicines for hypertension in children.

12.4 Review of safety and efficacy and place in therapy of dopamine in children.

12.5 Review of antithrombotic medicines for use in children.

12.6 Review of use of, and need for lipid lowering agents in children (includes consideration of lipodystrophy in children treated for HIV).

Section 13 Dermatological preparations

13.2 Review of the usefulness of gentian violet in children (trials are in progress — Wellcome Trust trial in Malawi, trial in conjunction with WHO in Pakistan).

13.2 Review of semi-solid formulations of polyvidone iodine topical (ointment 10%) for use in children.

13.4 Review need for astringent preparation for use in children with deletion of aluminium acetate solution (need in humid climates?)

13.6 Review of alternatives to benzyl benzoate for use in younger children (possible role for sulphur based preparations in younger children).

Section 14 Diagnostic agents

14.2 Review of appropriate radiocontrast media for use in children.

Section 16 Diuretics

Review efficacy, safety and place in therapy of mannitol in children.

Review efficacy, safety and place in therapy of spironolactone in children.

Section 17 Gastrointestinal medicines

17.1 Antiulcer drugs: review and preparation of application for inclusion of omeprazole (or other proton pump inhibitor).

17.2 Antiemetics: review and preparation of application for inclusion of domperidone as alternative to metoclopramide.

17.2 Antiemetics: review and preparation of application for inclusion of a 5HT3 antagonist (e.g. ondansetron) as alternative to metoclopramide.

17.4 Laxatives: review and preparation of application for inclusion of lactulose as laxative for children.

Section 18 Hormones and other endocrine medicines

18.1 Review of Section 18.1 (adrenal hormones and synthetic substances) with application for addition of fludrocortisone for the treatment of Addison's disease.

18.5 Review of oral antidiabetic agents for use in children, recognizing the changing epidemiology of disease and increasing public health importance of obesity and Type II diabetes in children.

18.8 Review of use of propylthiouracil in children and appropriateness of carbimazole as an alternative for use in children.

Section 20 Muscle relaxants

Review of choice of appropriate non-depolarising muscle relaxants for use in children.

Section 21 Ophthalmological preparations

Review of anti-infective eye drops, identifying which conditions and treatments are most appropriate for use in children.

Section 24 Psychotherapeutic medicines

24.1 Review of use of risperidone in children for use in psychotic and other psychiatric disorders, with application for the next committee meeting.

24.2 Review of medicines used to treat bipolar disorders in children, particularly considering the role of lamotrigine and other newer agents.

24.3 Review of medicines to treat anxiety disorders in children, with focus on short-acting benzodiazepines such as lorazepam.

24.4 Review of treatment of OCD in children, with appropriate application for the next committee meeting.

Section 25 Respiratory medicines

25.1 Review the place of ipratropium use in children, with application for the next meeting if appropriate.

25.1 Review of the place in therapy of oral salbutamol preparations in children, with particular emphasis on efficacy and safety in asthma and in the wheezy child with acute respiratory tract infection (may reduce the prescription of antibiotics in these children).

25.1 Review the place in therapy of long acting beta-agonists (LABA) in children and preparation of application for next meeting if appropriate.

Section 27 Vitamins and minerals

Review of entire Section, assessing burden of disease and appropriate vitamins and minerals for all paediatric age groups, and the role and composition of multivitamin preparations. Review to include consideration of calcium, calcitriol, magnesium, phosphate, selenium and zinc.

Appendix 6

List of individuals and institutions sending in comments to the Subcommittee

Individuals:

Mario Abinun, Consultant Paediatric Immunologist, Newcastle General Hospital, Newcastle upon Tyne, UK

Prof. K.C. Agba, Ministère de la Santé, Togo

Dr Sean Beggs, General Paediatrician, Paediatric Clinical Pharmacologist, Royal Hobart Hospital, University of Tasmania, Hobart, Australia

Dr Frédéric Bernard, Hémato Immuno Oncologie Pédiatrie, Pédiatrie 3, Hôpital Arnaud de Villeneuve, Montpellier, France

Pr A.A. Bousfiha, Président de l'Association Hajar de soutien aux patients Atteints de DIP, Casablanca, Morocco

Dr Jane Briggs, Management Sciences for Health

Dr Xuanhao Chan, International Pharmaceutical Federation Project Coordinator

Dr Charlotte Cunningham-Rundles, Professor of Medicine, Paediatrics and Immunobiology, USA

Dr M. Duddridge, UK

Dr Espanol and Dr Soler, Spain

Dr Madlen Gazarian, Head, Paediatric Therapeutics Program, Senior Lecturer, School of Women's and Children's Health, University of New South Wales, Paediatric Clinical Pharmacologist and Rheumatologist, Sydney Children's Hospital, Sydney, Australia

Hasmi Laila, Medical student, Faculty of Medicine and Pharmacy of Casablanca, Hassan II University, Morocco

Dr Koné Issa

Dr E. Kaminski, Consultant Immunologist, UK

Dr B. Ahmed Ali Magboul, Sudan

Dr Fethi Mellouli, Centre National de Greffe de Moelle Osseuse, Tunis, Tunisia

Dr Michels, German Working Party of Paediatric Rheumatology

Dr Tony Nunn, Clinical Director of Pharmacy, Royal Liverpool Children's NHS Trust and Associate Director, Medicines for Children Research Network, University of Liverpool, UK

Prof. Dr. med. H.H. Peter, Abteilung Rheumatologie und Klin. Immunologie, Medizinische Univ.-Klinik, Freiburg, Germany

Dr C. Poets, German Society of Neonatology and Paediatric Intensive Care

Dr H.W. Seyberth, University of Marburg, Germany

Dr A. Sidi Mohamed, Chef service pédiatrie, CHN Nouakchott, Mauritania

Dr Wendy Snowden, Clinical Development ID MDC, GlaxoSmithKline R&D, Bdg 38 -2/30, Greenford Rd, Greenford, Middlesex, UB6 0HE, UK

Dr Elizabeta Zisovska, Skopje, Republic of Macedonia

Institutions:

Asia Pacific Immunoglobulin in Immunology Expert Group

International Union of Immunological Societies

Médecins Sans Frontières

The Elizabeth Glaser Pediatric AIDS Foundation

The International Pharmaceutical Federation (FIP)

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The selection and use of essential medicines.
Report of the WHO Expert Committee
(including the 15th Model List of Essential Medicines)
WHO Technical Report Series, No. 946, 2007 (162 pages)

Pocket book of hospital care for children.
2005 (378 pages)

The international pharmacopoeia, fourth edition.
Volume 1: general notices; monographs for pharmaceutical substances (A–O)
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.
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Volume 1: 1997 (244 pages)
Volume 2: Good manufacturing practices and inspection.
2nd updated edition, 2007 (in print)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.
Fortieth report.
WHO Technical Report Series, No. 937, 2006 (461 pages)

International nonproprietary names (INN) for pharmaceutical substances.
Cumulative List no. 11
2004 (available in CD-ROM format only)

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This report presents the recommendations of the Subcommittee of the WHO Expert Committee responsible for the WHO Model List of Essential Medicines. The task of this Subcommittee was to draw up the first WHO Model List of Essential Medicines for Children. The first part of the report contains a summary of the Committee's considerations and justifications for the inclusion of particular medicines in the Model List for Children. Appendices to the main report include the first WHO Model List of Essential Medicines for Children, a list of all the items it contains sorted according to their 5-level Anatomical Therapeutic Chemical (ATC) classification codes and a summary of medicines to be reviewed before the next meeting of the Subcommittee.

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