



make medicines *child size*

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# **Technical consultation on the use of pharmacokinetic analyses for paediatric medicine development**

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



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## Abbreviations

ARV	Antiretroviral
BSA	Body surface area
EMA	European Medicines Agency
ETH	Ethambutol
FDC	Fixed-dose combination
HIV	Human immunodeficiency virus
INH	Isoniazid
NIH	National Institutes of Health
PAWG	Paediatric Antiretroviral Working Group
PD	Pharmacodynamic
PK	Pharmacokinetic
POPPK	Population pharmacokinetic
PZA	Pyrazinamide
RIF	Rifampicin
TB	Tuberculosis
TI	Therapeutic index
WARN	World Antimalarial Resistance Network

## Executive summary

In May 2009, a group of paediatric clinical pharmacologists, paediatric pharmacists, epidemiologists and representatives from the European Medicines Agency (EMA) and the US National Institutes of Health (NIH) attended a meeting hosted by WHO to discuss the different approaches that have been used to define optimal doses of medicines to treat HIV, malaria, tuberculosis (TB) and pneumonia in children, including the use of pharmacokinetic and epidemiological modelling. "Optimal doses" should result in appropriate efficacy and safety, but also need to take into account the changing pharmacokinetics that occur in children. Strategies used to develop simplified dosing regimens for the treatment of HIV and malaria within national control programmes were also reviewed.

Current knowledge gaps in the development of optimum medicine dosages as well as limitations in the current product development process were identified for the priority disease areas of HIV, TB, malaria and pneumonia in children. Opportunities to harmonize the different modelling approaches were explored and proposals were made for future work in this area. This report summarizes the meeting discussions, provides an overview of the outcomes of the meeting, and elaborates on the need for further research.



The following general issues were agreed:

- Pharmacokinetic modelling is an integral part of drug development, but it is only one aspect of the process of modelling dosing variability and drug exposure. Variability of drug exposure may also occur due to tablet size, use of tablet fractions and different dosing strategies. There is a need for an integrated approach to assess safety and efficacy of paediatric dosing at a time when organ development and steep growth creates additional variability in real-life exposure, including in the drug development process and post-marketing assessment of new medicine doses and formulations for children.
- The need for paediatric PK data and dose finding studies for particular medicines is related to the therapeutic index or therapeutic range of the medicine, that is the ratio of the toxic to the therapeutic dose. Medicines with a narrow therapeutic index need to be administered more accurately than drugs with a wide therapeutic index and this information could be considered in developing a 'risk management' approach for providing dosing instructions for medicines use in children in resource-poor settings. It was agreed that the WHO Model List of Essential Medicines for Children should be evaluated to determine risk categories for the individual drugs based on available data, to highlight knowledge gaps, research priorities and determine appropriate dosing strategies (e.g. by height, weight or body surface) for essential paediatric medicines.
- All doses of medicines for children should be calculated according to body weight, but the availability of weighing scales in health-care facilities in developing countries is often limited. Alternative methods of estimating or calculating body weight were discussed, including height or length, mid-upper arm circumference and segmental (specific bones) lengths. Data and growth curves from developed countries may be informative to establish correlations. It was agreed that a prospective study should be done in multiple countries in order to collect sufficient data to establish the validity of alternatives to estimate weight.
- A process should be established that ensures that the 'optimum dose' can be updated during the 'life' of a product, by systematic data collection from programmes of medicine delivery. Data collection should be ongoing, and be part of all programmes.
- Further research is needed to understand how to improve adherence and compliance in relation to medicines use in children. This might include palatability of the drug, the clarity of instruction and the packaging. There is some evidence from work undertaken with antimalarial medicines to support the use of blister packs to improve compliance.



- A consensus was reached for establishing a paradigm for the ideal dosage form and dosage regimen for treating priority conditions in children. The rationale was to provide a regimen that was simple to remember and would be consistent across diseases, would be relatively easy to administer by a trained health-care worker or caregiver and would have the best likelihood of compliance with the intended therapeutic effect:
  1. whenever possible, solid oral formulations suitable for administration to children (e.g., dispersible, scored sufficiently to permit accurate dose division) should be developed;
  2. the number of tablets, capsules or dosage units should ideally be limited to two per scheduled administration;
  3. depending upon the risk category and target exposure, several dosage strengths may be required to achieve the needed precision;
  4. the number of weight bands required to achieve target exposures within safe limits will be informed by the risk category as well as the available dosage forms and target exposure.

## **Introduction**

The global mortality rate in children under five is a significant problem, particularly in the disease groups of HIV, tuberculosis, malaria and pneumonia. The World Health Organization stipulates that children should be given medicines that have been appropriately evaluated for their use in paediatric populations, since the pharmacokinetics and pharmacodynamics of drugs in children are known to differ from those of adults. Most medicines for use in children were originally developed for adults, with little or no research performed specifically in paediatric populations. The lack of data on the optimum target dose and therapeutic dose range for paediatric medicines and the unavailability of appropriate paediatric dosage forms result in children frequently being prescribed medicine doses that are inappropriate for their needs. Sub-optimal dosing is a major determinant of treatment failure in individual patients and may drive the development of drug resistance in the population. Conversely, overdosing, may lead to serious adverse effects in individuals and may negatively affect the reputation of an efficacious medicine in communities, thereby affecting use and compliance.

The aim of this technical consultation was to bring together paediatric clinical pharmacologists, paediatric pharmacists, epidemiologists and representatives from EMEA and NIH to review different pharmacokinetic modelling approaches and strategies for the development of suitable dosage regimens and their contribution to paediatric drug development in the areas of HIV, tuberculosis, malaria and pneumonia.

## Meeting objectives

- To identify the common principles and any significant differences in the methods that are used for modelling optimal doses of medicines for children, specifically medicines for the treatment of HIV, tuberculosis, malaria and pneumonia.
- To define, if appropriate, a preferred approach.
- To determine the priority medicines and disease areas for future assessment.
- To identify research needs for the future development of dosing aids for children.

## Summary of meeting discussions

The following presentations were made (copies of slides are available on request):

- *Professor Tony Nunn*: a review of the work undertaken by the WHO Paediatric Antiretroviral Working Group (PAWG) for the development of priority fixed-dose antiretroviral (ARV) combinations and the use of a simple weight band-based dosing approach for the administration of paediatric HIV treatments.
- *Dr Edmund Capparelli*: the pharmacokinetic modelling technique used to examine the results of the recommended paediatric dosing for actual and potential ARVs and fixed-dose combinations FDCs based on the generic dosing tool developed by the PAWG.
- *Dr Greg Kearns and Dr Susan Abdel-Rahman*:
  1. a review of the pharmacokinetic modelling technique used to determine the range of paediatric exposures expected in infants and children after fixed-dosing of isoniazid, rifampicin, pyrazinamide and ethambutol;
  2. the preliminary results of an investigation to determine paediatric-specific values of pharmacokinetic parameters for amoxicillin;
  3. an overview of a new and potentially more accurate method for estimating total body weight in children.
- *Dr Dianne Terlouw*: a review of a method to optimize tablet strength and dosing regimens for new fixed-dose antimalarials for treating falciparum malaria using available knowledge on dose levels, including the reasons for the "epidemiological" modelling that was carried out to translate weight-based recommendations to age-based dosing regimens for programmatic use.



- *Dr Anna Ridge*: a review of weight-estimation methods and dosing aids that have been used to help calculate medicine dosages and aid the prescribing and administration of medicines to children.
- *Dr Charles Larson*: the use of colour coding medicines by weight in resource-poor settings.
- *Dr Mats Karlsson*: estimating cumulative variability of PK properties and drug delivery strategies by size of the therapeutic index.

## **Overview of methods used to develop HIV/ARV fixed-dose combinations and a weight-band dosing regimen**

### ***Background and modelling technique***

In 2006, a Paediatric Antiretroviral Working Group was convened to identify priority combinations of HIV medicines for children and to develop dosing tables to allow the simple dosing of FDCs based on the weight of a child. The premise was that HIV care delivered by health-care workers/medical officers requires medicines that are easy to use and dosing guidance that is easy to follow. A priority list of single, dual and triple ARV products for paediatric HIV treatment were identified and a generic dosing tool that could be used to assess the accuracy of the intended dose to be delivered was developed.<sup>1,2</sup> From this exercise simple dosing tables based on weight bands were developed for the FDC products.

The WHO 'generic tool' for assessing paediatric ARV dosing is a spreadsheet that allows for manipulation of the intended delivered dose given for any ARV for a range of weight bands and their corresponding estimated body surface area (BSA). The tool is also useful for examining whether the intended dose is above or below the target dose recommended. It can be adapted for single, dual or triple combinations.

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- 1 World Health Organization. Preferred antiretroviral medicines for treating and preventing HIV infection in younger children. Available at:  
<http://www.who.int/hiv/events/paediatricmeetingreport.pdf>
  - 2 WHO generic tool for assessing paediatric ARV dosing. Available at:  
<http://www.who.int/hiv/paediatric/generictool/en/index.html>

The generic tool can be used to assess existing or potential products and to determine dosing schedules for any particular single or combination product. It is based on the following assumptions:

- BSA is converted to weight, using a weight-based formula for predicting BSA from weight, that has been developed and validated using demographic and anthropometric measurements of 459,036 children collected in 560 anthropometric surveys between 1992 and 2006;
- the tablet strength, maximum dose, formulation and frequency of administration can be altered;
- the number of tablets is entered into the spreadsheet;
- the dose delivered for each weight is calculated (number of tablets x tablet strength/weight).

The generic dosing tool was devised to allow the development of weight-banded dosing tables of drug combinations and doses in order to assist programme implementation. It is proposed that there be the same number of tablets for dose delivery in each weight band regardless of drug or combination of drugs. A 'public health' approach to dosing was followed to allow harmonization of the tablet regimens. However, this compromise may mean that in some cases over- or under-dosing may occur, especially in infants, due to differences in developmental pharmacology.

Population pharmacokinetic modelling and simulations have been undertaken to evaluate some of the recommended ARV treatment regimens. These studies were based on PK data from various paediatric populations and were analysed using a population pharmacokinetic (POPPK) model. The advantages of using POPPK modelling is that a broad spectrum of subjects can be included, and covariates for size, age, genotype, binding proteins, diet and interacting drugs are incorporated into the model. Data are available from birth for non-nucleoside reverse transcriptase inhibitors allowing the accurate dosing of nevirapine in children. However, recommendations for optimal lopinavir dosing in very small children are still uncertain; and more information is required for other protease inhibitors.

The use of population PK modelling and simulation can be used to help refine the WHO weight-band dosing criteria, which will ultimately result in improved ARV dosing.

### ***Issues identified***

- Simplified dosing strategies for paediatric ARVs can be developed through a collaborative process between clinical pharmacologists, paediatricians and technical advisers for the implementation of public health programmes.
- the dose of an antiretroviral medicine that is initially approved by regulatory authorities may not be the optimum dose for children. It will have to be based on the data available at the time of registration, which is often limited due to a lack of specific PK studies in the target population.
- There is a need to integrate paediatric pharmacology and ARV exposure-response knowledge.
- Field validation of the weight-band dosing tables is required.
- WHO is expected to provide dosing guidance from birth onwards. However, there is currently a lack of PK data for determining the optimum doses of protease inhibitors for neonates and children < 2 years. There is also a need to develop strategies for the collection of exposure data.
- The impact of malnutrition on the recommended ARV doses is currently not known.

### **Overview of methods used for developing TB fixed-dose combinations**

#### ***Background and modelling technique***

In high incidence countries, 20-40% of the TB cases are in children. The youngest children have disproportionately higher rates of morbidity and mortality. There is a paucity of pharmacokinetic data; only 1 study of new agents for TB in the past 15 years has included children. In July 2008, WHO convened a task force to evaluate the dosage regimens currently recommended by WHO for the treatment of children with TB. A comprehensive review of the first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) was undertaken with respect to age-appropriate guidelines for their dosing and use. The task force considered the importance of adherence and compliance in drug regimens to treat paediatric TB and identified the need to produce an age-appropriate solid FDC, to permit age-appropriate drug dosing in a precise and simple manner.



The new daily dosing regimens that have been proposed for children > 3 months are<sup>1,2</sup>:

- Ethambutol (ETH): 20 mg/kg/day (range 15-25).
- Isoniazid (INH): 10 mg/kg/day (range 10-15).
- Rifampicin (RIF): 15 mg/kg/day (range 10-20).
- Pyrazinamide (PZA): 35 mg/kg/day (range 30-40).

These are consistent with other guidelines, such as those produced by the American Academy of Pediatrics.

Pharmacokinetic simulations were performed to determine the range of paediatric exposure expected in infants and children after administration of specified doses of isoniazid, rifampicin, pyrazinamide and ethambutol, using pharmacokinetic parameter estimates derived from previously conducted paediatric studies. Where necessary, data from adult studies were used to derive estimates of absorption rate constant and oral bioavailability.

The following assumptions were made about the PK parameters used in the simulation model:

- The PK parameters derived from primary and secondary medical literature offer a reasonable approximation of those that would be observed in the infants and children receiving the FDC under evaluation.
- The PK parameters represent values that approximate those that would be observed after repeated drug administration.
- The PK parameters used for the simulation of any given drug represent values that approximate those that would be observed with concomitant administration of the other drugs (i.e. with no accounting for drug-drug interactions).

The pharmacokinetic simulations were then used to propose two FDCs that would produce levels of systemic exposure predictive of efficacy and safety in children ranging in weight from 5 to 30 kg, assuming a single daily dose and not breaking the tablet in more than half).

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1 World Health Organization, 2006. Ethambutol efficacy and toxicity: literature review and recommendation for daily and intermittent dosage in children.

2 World Health Organization, 2008. Report of the meeting on TB medicines for children. Available at:  
[http://www.who.int/selection\\_medicines/committees/subcommittee/2/TB.pdf](http://www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf)



- A 3-drug FDC: INH 150 mg + PYR 400 mg + RIF 250 mg.
- A 4-drug FDC: ETH 250 mg + INH 150 mg + PYR 400 mg + RIF 250 mg.

No FDCs on the market currently meet these specifications. Combinations of available FDCs were therefore assessed to determine whether they would result in sufficient exposure of the components. This analysis showed that the combinations of currently available FDCs required to produce the recommended daily dosing levels for the individual components resulted in a high pill burden and a need to be adjusted to avoid a daily INH dose of >15 mg/kg/day, which is associated with a greater tendency to produce hepatotoxicity. Very few of the existing products could be combined in such a way to achieve appropriate doses without risk of toxicity, and some resulted in significant under-dosing, reinforcing the need for the development of the 'ideal' paediatric FDCs.

### ***Issues identified***

- Paediatric-specific PK data for antitubercular agents from large, well conducted clinical trials spanning the continuum of the paediatric age spectrum do not generally exist. Rather, paediatric PK data are available from only a few published studies, most with small subject cohorts which restricts the ability to accurately determine the true variability associated with specific PK parameters for each of the drugs. Future studies of these drugs should be designed in such a fashion as to eliminate these knowledge gaps.
- Modelling based on limited PK data in children can be supplemented to a certain extent with information from adult studies
- However, the results show wide variation that may be due to the preparation used or variability in the dose – plasma concentration relationship consequent to factors pertaining to liberation of active drug from a given formulation and also, both age-dependent (i.e. developmental) and inter-subject differences in processes which govern drug absorption, distribution, metabolism and/or excretion.
- Matching recommended doses from the modelling exercise to currently available products results in regimens with a high pill burden. A high pill load increases the risk of the wrong dose and decreases compliance and adherence.
- Ideally, the simulations should be validated by exposure data collected from subjects of different age ranges, with documentation of the preparation administered. A population pharmacokinetic study of the existing TB combinations dosed appropriately is urgently required.

## **Overview of methods used for developing an antimalarial age-based dosing regimen**

### ***Background and modelling technique***

In contrast to HIV and TB, malaria is an acute illness, usually treated with 3-day regimens. The current FDCs available for children include artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine. The combination of artesunate + sulphadoxine-pyrimethamine is available only as loose tablets, but this combination is no longer a first- or second-line choice in most regions. Challenges in the treatment of malaria are that the current recommended dosages for children are extrapolated from adult doses and are likely to be inaccurate, and there is a high pill burden, particularly in older children, due to a lack of suitable FDCs for children.

Drug doses in children are typically calculated according to body-weight. However, weight-based dosing in countries where malaria is endemic is challenging because functioning weighing scales are scarce, access to formal health services is limited and a significant proportion of treatment occurs at home using antimalarials bought from shops and street vendors.

The methods used to establish regional age-based dose regimens for the treatment of uncomplicated falciparum malaria have been based on "epidemiological" modelling, carried out to translate weight-based recommendations to age-based dosing regimens for programmatic use in the target population<sup>1</sup>. It is based on the principle that the recommended mg/kg starting dose is correct, based on efficacy and safety data and PK data from paediatric populations. This weight-based information is then converted to age-bands, using newly generated regional weight-for-age reference curves from compiled country-level, population-representative nutritional, data. Age-based dosing requires a drug with a relatively large therapeutic index, because it considerably increases the variability in dose intake, which will lead to some under- or over-dosing, particularly in drugs with relatively narrow therapeutic indexes.

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1 Taylor WR et al. 2006. Use of weight-for-age-data to optimize tablet strength and dosing regimens for a new fixed-dose artesunate-amodiaquine combination for treating falciparum malaria. *Bulletin of the World Health Organization*. **84** (12), pp. 956-964.

The determining factors for the accuracy and applicability of age-based dosing include:

- availability of appropriate tablet strengths/scoring;
- knowledge of the therapeutic dose range/therapeutic index.

### ***Issues identified***

- There is a paucity of PK/PD data for antimalarial treatments in children; the mg/kg drug dosages used to inform the age-band model were based on dosages for children extrapolated from adult PK data or clinical trials. Efforts are being made by the Gates funded WARN consortium to address some of these issues.
- There is concern that as exposure/efficacy relationships for antimalarials are not clearly defined, and current recommended dosages for antimalarial treatments for children may be too low, e.g. dosing of the artemisinin components in several FDCs is close to the minimum known effective dose of 2 mg/kg/dose. A consequence of this potential underdosing would be an increase in the likelihood of resistance in the target population.
- Open access to all individual-level PK data is required for dose optimization as well as further PK studies in children.

## **Overview of methods used for developing the optimum strength of amoxicillin for a simplified dosing regimen for the community treatment of pneumonia**

### ***Background and modelling technique***

There is evidence to show that community-based treatment with oral amoxicillin is effective to reduce mortality from pneumonia in children. The current WHO recommended dose for amoxicillin is 50 mg/kg/day divided into two doses. To facilitate availability and use, WHO is exploring the potential value of a 'public health pack' consisting of a flexible solid dosage form of amoxicillin for use in children in a variety of settings as first-line treatment of pneumonia. Taking account of the need for a simplified dosing regimen, the question addressed in the modelling so far is to define the ideal strength of a product to be included in a pack, to allow administration to children of a wide range of weight and ages but with minimal manipulation.

An *in silico* simulation was undertaken to determine paediatric-specific values of pharmacokinetic parameters for amoxicillin, to inform the assessment of tablet strength.

The initial results show that:

- the greatest PK variability is likely to be associated with absorption which, based on existing data from adults, is likely to be dose-dependent (i.e. non-linear);
- age-associated changes in clearance and apparent volume of distribution appear predictable based on the impact of development on renal function and body composition;
- based on published *in vitro* PD surrogate endpoints, amoxicillin doses ranging between 45 and 90 mg/kg per day, divided twice daily for infants and children would appear to produce adequate systemic exposure to adequately treat the majority of susceptible pathogens causing uncomplicated bacterial pneumonia.

The next step will be to develop a profile of a pack size and presentation useful for the treatment of community-acquired pneumonia in children aged 0 to 6 years.

## **Weight estimation methods and dosing aids**

### ***Weight estimation methods***

Most drug dosages for children are calculated on a per kilogram basis, therefore knowing a child's weight is important for determining the correct dose. Many different methods exist for the estimation of a child's weight, ranging from age-based formulas to height-based methods using a specially designed tool. The most commonly accepted method for weight estimation in children aged 1-10 years in Europe, South Africa, Australia and New Zealand is the age-based formula ( $2 \times [\text{age in years} + 4]$ ), as recommended by the Advanced Paediatric Life Support course<sup>1</sup>.

The majority of the validation and comparison studies using these different methods have been undertaken in developed country settings. Limited data exist from developing country settings. Most evidence indicates that weight estimation methods need to be tailored to the country population in which they are used. The clinical significance of the potential under- or over-dosing in the administration of medicines to children as a result of using the various weight estimation methods has not been reported.

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1 Advanced Life Support Group. Advanced Paediatric Life Support: The Practical Approach. 4<sup>th</sup> ed. London, British Medical Journal Books/Blackwells, 2005.



In comparative studies, the most accurate methods for estimating weight have been found to be the length-based methods: the Broselow tape (patient's height as predictor) and the Devised Weight Estimation Method (patient's height and body habitus as predictors). The Broselow tape is the most validated method, with some data from developing country settings. Across the studies undertaken in developed countries it shows a general tendency to underestimate weight, an inaccuracy that increases with increasing weight. However, in an sample of children in India, whose actual weight was >10 kg, the Broselow method overestimated weight by more than 10%. A correction factor of 10% that was recommended still requires prospective validation. The contribution of such a correction factor to improve dosing accuracy will be related to the therapeutic index of the drugs in question. Height-based dosing may be challenging for drugs bought over-the-counter when the sick child may not be present, but could be suitable for primary care centres and mass treatment campaigns, as has been done with drugs like albendazole and praziquantel.

### **Dosing aids**

Preliminary results of a systematic review show limited published evidence of the benefits of various dosing aids for the administration of medicines for children<sup>1</sup>. One small randomized controlled trial conducted in the UK assessed a dosing tool for the prescribing of analgesia to children, using a simulated prescription chart. The results showed that the tool increased the number of prescriptions and improved accuracy. A number of studies suggest that the oral dosing syringe may be the best device for the delivery of liquid medications. The accuracy of dosing liquid suspensions using measuring spoons is very poor, with significant overdosing being a recurrent problem. However, the clinical implications of the potential overdosing have not been reported.

The use of blister packs for the treatment of malaria have been used to improve adherence to the treatment regimen<sup>2</sup>.

### **Colour coding**

Colour coding, a universal colour system for different weight-bands/ages, has been proposed as a way to improve the administration of medicines to children. A specially designed colour coded tape, based on height-weight relationships, is used to assign a colour code to an individual patient. The patient's height will correspond to a particular coloured section of the tape. If the patient's height corresponds to the

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1 Ridge A. 2009. Weight-Estimation and Dosing Aid Review (unpublished)

2 Orton LC, Barnish G. Unit-Dose Packaged Drugs For Treating Malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD004614. DOI: 10.1002/14651858.CD004614.pub2.



colour section which is blue, for example, this colour will assigned to the child for the duration of its hospital stay. All treatment interventions will be based on the colour code. This colour code is used to map the patient to the correct dosages of medicines and equipment. The medications are labelled with special colour-coded dosing labels to match the coloured sections on the tape. The tape needs to be validated in the target paediatric population before its use to ensure accuracy.

### ***Weight-based versus age-based dosing regimens***

While weight-based dosing is considered the optimal approach to assure accuracy of dosing there are considerable practical constraints. Many resource-poor settings lack functioning weight scales and medicines are often bought over-the-counter without contact with the health system.

Age-based dosing is likely to be less accurate than height-based dosing but it is more appropriate for settings where drugs that are bought over-the-counter without the child being present, as happens with antimalarials for uncomplicated malaria, and low risk drugs with a relatively wide therapeutic index. To improve dosing accuracy with age-based dosing regimens they ideally need to be tailored to the target population, using appropriate weight-for-age reference data that take into account regional variations in body-weight and composition. Because neonates, infants, children and adolescents have distinct differences in physiological development, it seems reasonable to identify age-based dosing regimens, especially given the ease with which this approach can be used in practice.

For HIV treatment and management, weight information is imperative, since ARVs have a narrow therapeutic index, and weight change is used to monitor response to treatment. These recommendations can be generalized to other medicines with narrow therapeutic indexes. In cases where weight-based dosing is required, dosing regimens with appropriate tablet strengths and pre-determined weight bands will help simplify dosing and guide appropriate treatment guidelines.

The optimal approach for accuracy of dosing was considered to be weight-based dosing, but the practical constraints that may make this impossible were noted. Age-based dosing regimens need to be tailored to the target population, using appropriate weight-for-age reference data that take into account regional variations in body-weight and composition. Because neonates, infants, children and adolescents have distinct differences in physiological development, it seems reasonable to identify age-based dosing regimens, especially given the ease with which this approach can be used in practice. A distinct disadvantage is that this approach assumes that maturational effects on drug deposition are consistent within each of the age-based categories. This approach imprecisely reflects the substantial

pharmacokinetic variability over wide age ranges. Another problem with age-based dosing is the fact that in some developing countries the true age of a child cannot be determined.

For medicines that are bought over-the-counter, age-based dosing is more appropriate. For HIV treatment and management, weight information is imperative. Children must be weighed at their clinic visits in order to monitor response to treatment. This requirement can be generalized to other medicines with narrow therapeutic indexes.

A problem with using estimates of weight or age for dosing is that they add variance to the PK variables (e.g. exposure, peak concentration) which determine the dose dependent efficacy and safety of a medicine. The use of either age- or weight-bands will further increase this variability. For active substances with biologically small inter-individual variability in these parameters and a wide therapeutic index, the added variability will be less of a problem than with active substances with a narrow therapeutic index. Therefore the nature of the therapeutic index of a medicine will determine if it can be safely dosed by age or weight. In principle, medicines with a wide therapeutic index could be safely dosed by age. Those with a narrow therapeutic index would need to be dosed by weight.

### ***Issues identified***

- None of the identified weight estimation methods has been validated in paediatric populations with very high rates of malnutrition.
- Whether it is possible to identify a minimum age that is reasonable for age-based dosing, given uncertainty in weight-age relations especially in children < 5kg.
- WHO recommends the use of oral solid dosage forms over liquid dosage forms for stability, dosing and administration issues where possible. However, until liquid formulations are replaced, an oral dosing syringe should be used for administration of liquids to children.
- Several different methods of colour coding exist. There are concerns that the systems could be mixed up, leading to medication errors and adverse events.
- Field testing of the new method for estimating body weight in children in resource-poor settings and paediatric populations with high levels of malnutrition is required.



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- The potential for assessing all the medicines on the WHO Model List of Essential Medicines for Children to define the approximate therapeutic index (i.e. narrow/high risk, wide/low risk or not known) as the basis for making more general recommendations about whether dose should be according to weight or age.

The following common principles for determining optimal dosage forms/strengths of medicines for children were suggested:

- Weight-based dosing should be defined, with a buffer between minimum effective and maximum tolerated dose. The lowest recommended dose must exceed the minimum effective dose in order to minimize the risk of drug resistance and/or under-treatment possibly associated with disrupted treatment adherence (e.g. missed dose);
- develop weight-based dosing recommendations with a simple dosing regime, preferably once or twice daily as dictated by the anticipated pharmacokinetic properties of a given drug;
- there should be ideally no more than 2 "tablets" per dose (as flexible oral solid dosage form), and these should be suitable for all ages;
- efforts should be made to minimize the number of different dosage strengths. At least one paediatric and one adult strength should be available.

## **Research needs**

The following research priorities were discussed:

- To explore and develop integrated PK/PD and other 'epidemiological' modelling tools, to capture the cumulative variability at the different stages from dose intake linked to dose strategy, and nutritional status to pharmacokinetic and dynamic properties. Plans are being developed to explore this for malaria related PK/PD and epidemiological modelling efforts.
- To assess the medicines on the WHO Essential Medicines List for Children and define the approximate therapeutic index (i.e. low/moderate/high risk, or not known) as the basis for making more general recommendations about whether dose should be according to weight or age. In principle, medicines with a wide therapeutic index (low risk) could be safely dosed by age, whereas doses with a narrow TI likely require dosing by weight-bands.



- To develop a tool that supports the decision-making process to determine and recommend suitable dosing strategies and regimens using weight-, height- and or age-bands based on the available TI and above mentioned risk categories.
- To conduct field assessments of the dosing strategy and dosing delivery tools
- Weight-band FDC dosing tool for HIV medicines with high risk TI category:
  - Age-band dosing tool for medicines with low risk TI category.
  - Delivery tools for impact: e.g., special blister packs, pictograms.
- Need for PK data from 'special groups', such as infants < 6 months of age and malnourished children to address the following issues:
  - Effect of malnutrition and/or multiple co-morbidities on drug absorption.
  - Effect of malnutrition on weight-based dosing.
  - Drug absorption in children under 6 months of age.
- Impact of food on the absorption of medicines in children.
- Determinants of adherence to medicines in children.
- Is there a need to have different recommendations for prophylactic regimens and treatment regimens for HIV and TB drugs? Is there a significant difference between exposure in these scenarios?
- Where ideal FDCs are not yet available, is there a safe and practical way of tailoring existing formulations to the optimum recommended doses?

### **Next steps in paediatric drug development, implementation and dose optimization during the post-registration process**

After discussion, the following advocacy and facilitation roles were suggested to be taken up by the WHO Department of Essential Medicines and Pharmaceutical Policies (related to the paediatric dose optimization, drug development process, implementation and potential dose adjustment post-registration:

- Aim to develop consensus in the global community on criteria for paediatric product development and administration as specified in common principles for 'ideal' drugs (see above) so that there is as much consistency as feasible across disease areas.



- Advocate for more attention during drug the development process to the target population and end-users, as well as the likely dosing strategy and delivery process for new drugs and FDC products to end-users. Encourage the estimation of the therapeutic index/therapeutic dose range as part of the dose optimization process in addition to the target dose to support the development of a safe, effective, and user-friendly dosing strategy and regimen for use in control programmes, and integrate this process into the standard drug development process.
- Advocate and facilitate the assessment and modelling of pooled available individual level PK and PD data for paediatric dose optimization. Encourage stakeholders to share individual-level data that are currently not in the public domain, such as regulatory PK studies conducted during the drug development process. It is in the interest of public health that such data are made publicly available and included in PK and PD modelling efforts to advance the development of optimal medicines for children and support the development of post-marketing population PK surveillance.
- Encourage the conduct of Phase 3b effectiveness studies during the drug development process. These studies should assess the potential dose range and dose regimens that are suitable for use in control programmes, and evaluate the variation in dose exposure and drug levels, efficacy and safety that is expected to occur once the drug is registered and marketed. This is particularly important for drugs that are likely to be implemented using dosing strategies that are different from those used during the standard development process (e.g. age-based versus weight-based dosing of drugs aimed for use at community level).
- Ensure quality assurance and monitoring and evaluation components including population PK, efficacy, effectiveness and safety are integrated into implementation plans in the paediatric population to continually improve the available evidence base and inform potential future dose adjustments.
- Develop agreement on a feedback process to regulatory authorities and manufacturers to update dosing, toxicity and specific population use information. Encourage commitment to reassessment and adjustment of recommended doses of medicines after implementation of treatment strategies, based on evidence from post-marketing/Phase IV monitoring of efficacy, safety and effectiveness in target populations, as well as further PK and PD data.



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It is increasingly recognized that the inaccuracy of dosing in paediatric and adult populations can lead to increased resistance. The issue of inaccurate dosing, e.g. the risk of underdosing in large and obese adults needs further exploration, as the use of a single dose across the adult population and hesitancy to adjust doses accordingly may be responsible for driving resistance.



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## List of participants

### Temporary Advisers:

**Dr Susan M. Abdel-Rahman**, Associate Professor of Pediatrics, Director, Development Pharmacokinetic and Pharmacodynamic Core Laboratory, The Children's Mercy Hospitals and Clinics, 2401 Gillham Road, Kansas City, MO 64108, USA  
Tel: +1- 816 855 1759; E-mail: srahman@cmh.edu

**Dr Edmund Capparelli**, Pediatric Pharmacology Research Unit, University of California San Diego, 7910 Frost Street #360, San Diego, CA 92123, USA  
Tel: +1- 858-246-0009; Fax: +1- 858-246 0025; E-mail: ecapparelli@ucsd.edu

**Dr Steven Hirschfeld**, Associate Director for Clinical Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), 31 Center Drive, Room 2A03, MSC 2425, Bethesda, MD 20814 USA.  
Tel: +1-301 496 0044; Fax: +1-301 402 1104, E-mail: hirschfs@mail.nih.gov

**Dr Kalle Hoppu**, Director, Poison Information Centre, Helsinki University Central Hospital, P.O. Box 790 (Tukholmankatu 17), 00029 HUS (Helsinki), Finland  
Tel: +358 9 471 74 788, Fax: +358 9 471 74 702, E-mail: kalle.hoppu@hus.fi

**Dr Mats Karlsson**, Professor of Pharmacometrics, Dept of Pharmaceutical Biosciences, Uppsala University, Box 591 751 24 Uppsala, Sweden  
Tel: +46 18 4714105; Fax: +46 18 471 4003, E-mail: mats.karlsson@farmbio.uu.se

**Dr Gregory L. Kearns**, Professor of Pediatrics and Pharmacology, University of Missouri Kansas City (UMKC), 2401 Gillham Road, Kansas City, MO 64108, USA  
Tel: +1-816-234-3961; Fax: +1-816-855-1703; E-mail: gkearns@cmh.edu

**Dr Charles Larson**, Director, Centre for International Child Health, British Columbia Children's Hospital, Vancouver, BC, Canada  
Tel: +1-604-875 2000 ext 5642; mobile: (604) 868 7961; E-mail: clarson@cw.bc.ca

**Dr Efthymios Manolis**, Scientific Administrator, Scientific Advice and Orphan Drugs, Human - Pre Authorisation, Evaluation European Medicines Agency (EMA), 7 Westferry Circus, Canary Wharf, GB-London E14 4HB  
Tel: +44 207 523 7520; Fax: +44 207 523 7040; E-mail: Efthymios.Manolis@emea.europa.eu

**Professor Tony Nunn**, Clinical Director, Department of Pharmacy, Alder Hey Children's NHS Foundation Trust, and Associate Director, NIHR Medicines for Children Research Network, University of Liverpool, Eaton Road, GB-Liverpool L12 2AP  
Tel: +44 151 252 5314; Fax: +44 151 252 5675; E-mail: Tony.Nunn@alderhey.nhs.uk



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**Dr Dianne J. Terlouw**, Child & Reproductive Health Group, Liverpool School of Tropical Medicine, Pembroke Place, GB-Liverpool L3 5QA..

Tel: +44-151-705 3354; Fax: +44-151-705 3329; E-mail: d.j.terlouw@liverpool.ac.uk

#### WHO/HQ:

Dr Clive Ondari, Coordinator, HSS/EMP/MAR

Dr Suzanne Hill, HSS/EMP/MAR

Dr Anna Ridge, HSS/EMP/MAR

Dr Milan Smid, HSS/EMP/QSM

Dr Siobhan Crowley, HTM/HIV/ATC

Dr Malgosia Grzemska, HTM/STB/TBS

Dr Jose Carlos Martines, FCH/CAH/NCH

Dr Lulu Mussa Muhe, FCH/CAH/NCH

Dr Peter Olumese, HTM/GMP/CMR

Dr Adelheid Werimo Onyango, NMH/NHD/GRS

Dr Shamim Ahmad Qazi, FCH/CAH/NCH

## **Declaration of interests**

Participants in the Technical Consultation on the use of Pharmacokinetic Analyses for Paediatric Medicines Development reported the following relevant interests (in accordance with WHO procedures), for the period of the last three years:

- Dr Kalle Hoppu reported receiving one-time consultation fees from Lundback A/S, Denmark, and remuneration for a written clinical expert opinion for a regulatory submission from Oy Leiras, Finland Ab.
- Dr Edmund Capparelli reported receiving remuneration for consulting services from the following pharmaceutical companies: BMS; GSK; Cadence; Arpida; Pfizer; Abbott and Biosynexus.
- Dr Mats Karlsson reported being a partner in the pharmaceutical company Wellhagen and Karlsson HB and receiving research support for pharmaceutical investigations from a Swedish funding agency.
- Professor Tony Nunn reported receiving research grants from the National Institute of Health Research, UK.
- Dr Dianne Terlouw reported receiving research funding from DNDi that supports the development of drugs for tropical diseases, including malaria.
- Dr Steven Hirschfeld; Dr Gregory Kearns; Dr Charles Larson; Dr Efthymios Manolis; Dr Susan Abdel-Rahman reported no interests.