



make medicines *child size*

Agenda item:

**17th Meeting, Expert Committee on Selection
and Use of Essential Medicines.**

Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children

WHO Headquarters, Geneva, Switzerland

15-16 December 2008

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



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Executive summary

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

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

Declaration of interests

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

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



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- Professor Tony Nunn reported that his research unit receives grants from the UK National Institute for Health Research.
 - Dr Stephen Spielberg reported being the Principal Investigator of IPI.

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

Introduction

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

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

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

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

Meeting background

Meeting objectives

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

Preparatory work

1. A comprehensive review of the published literature, describing current technologies and dosage forms of medicines for children was carried out by Professor Peter York and Dr Amir Amani prior to the meeting.
2. A survey of end-user needs for preferred pediatric dosage forms was carried out by Ms Atieno Ojoo, and a draft document of these findings was prepared by Ms Atieno Ojoo and Dr Kalle Hoppu.
3. A literature review on socio-cultural issues that influence the acceptability of pediatric dosage forms was carried out by Drs Sienna Craig, Lisa Adams and Stephen Spielberg.

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

Summary of meeting discussion

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

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



available dosage forms for pediatric medicines, and identified recent innovations in dosage form designs and technologies.

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

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

Dr Stephen Spielberg provided an overview of the important socio-cultural issues to consider in improving pediatric dosage forms. He suggested that aspects such as acceptability, palatability, tolerance and compliance may vary widely between different cultural settings, and could be significantly influenced by socio-cultural issues.

Professor Rohini Fernandopulle presented a survey of care givers in Sri Lanka, outlining some of the problems faced when using currently available dosage forms of anticonvulsants to treat epilepsy in children.

Summary of evidence

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

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



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

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

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

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

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

Desirable attributes of a paediatric dosage form

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

- Minimal administration frequency
- Minimal impact on life style
- Minimum, non-toxic excipients

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

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

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

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

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

Socio-cultural aspects — Sienna Craig and Stephen Spielberg

A draft literature review (Sienna Craig et al.) on the sociocultural aspects of paediatric dosage forms highlighted the importance of cultural setting in suitability of dosage forms, with cultural differences noted in the understanding and expectations of treatment, duration of treatment, palatability, and acceptability of medicines.

Although the meeting acknowledged that cultural setting was important, it was noted that there was insufficient evidence to demonstrate a true variation in cultural acceptability. The possibility of producing a product that would be acceptable across multiple cultures through a platform technology that could be 'reformatted' to meet cultural norms, was therefore considered. Platform technologies are technologies that can be used to facilitate a broad range of application based activities. i.e. one formulation technology can be used for several active compounds.

Proposed recommendations

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

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

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

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

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

References

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability Annex 7, WHO Technical Report Series 937, 2006.

2. For severe disease conditions (e.g. neonatal sepsis), injections are the best existing option, but developments should include modified vial sizes or strengths to ensure suitability for all age groups (especially neonates) and packaging options that allow easy use. There needs to be development of injections and infusions that minimize risk of electrolyte overload. New developments in injection technology should be assessed, especially those that can be used in community or primary care settings.
3. For oral medicines requiring precise dose measurement or titration, the most 'suitable' dosage form should be based on use of a solid platform technology (multi particulate solid, including those that could be dispersed to form a liquid dose), rather than oral liquids. This can allow production of 'tailored' doses and strengths as well as preparation as a range of dosage forms such as tablets or capsules. Examples of current forms are mini-tablets and spherical granules (pellets). In terms of feasibility for the manufacturer, these dosage forms can be manufactured from standard excipients including those that are pre-mixed and suitable for a range of actives, and they have potential flexibility for constructing appropriate FDCs.
4. Techniques for 'difficult molecules' (defined using BCS classes) need to be developed/or evaluated, including manipulation (e.g. spray drying, micronization) prior to use with some platform that may produce suitable dosage forms for children.
5. As an alternative to injections in severely ill children or children unable to swallow, the use of rectal preparations for indications of severe malaria, pain and infection may be appropriate. Rectal preparations of analgesics exist but would need to be assessed for suitability for hot climates. There may be potential value in the development of some antibiotics as rectal preparations but not all would be suitable for this approach because of erratic bioavailability and/or cultural barriers.
6. Patch/transdermal drug delivery technology may be of use for medicines requiring constant plasma concentrations, but needs to be evaluated further. On the one hand, the technology is likely to remain comparatively expensive, and may not be appropriate for all climates, but there may be unpublished data available to facilitate their assessment and a full evaluation is warranted. It is important that patches are not cut, as this may alter release characteristics.

Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Annex 8, WHO Technical Report Series 937, 2006.

http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/index.html

7. Inhalational administration of substances is necessary for treatment of asthma and chronic lung disease, and has been evaluated for delivery of other molecules. There is a need for development of affordable and standardized devices for administration, although it is recognized that the technology may be complex.
8. Medicines for respiratory distress in neonates are available but in the case of surfactant are expensive and difficult to deliver. New approaches to delivering this product are needed.
9. Other less invasive methods of delivering drugs to children have been developed (buccal, nasal etc) but at present the technologies are either not generally affordable or available. Further study is warranted.
10. Researchers should ensure that full details on any new dosage forms used in paediatric clinical studies, are included in publications. A centralized accessible data base of published work on paediatric medicines, and where high -quality medicines in appropriate dosage forms are available, should be established.

Research needs

The following research needs were identified:

1. What particle sizes can be comfortably and safely ingested at different ages and developmental stages in children? [This aspect should be looked at from the perspective of both acute and chronic diseases.]
2. To optimize the acceptability of dosage forms, what standards should be set for 'granularity' (i.e. the size of the components of the medicine) and 'texture' or 'mouth feel' (i.e. the 'feeling' of a liquid, semi-solid or suspension in the mouth), taste and smell, at different ages and developmental stages.
 - For the products commonly used for priority diseases?
 - For other products (by BCS class)?
3. What are appropriate standards for palatability testing (where needed) in children, and how should it be done?
4. What evidence exists to define optimal frequency of dosing (and pill burden) in terms of impact on adherence and clinical outcomes? [Consider treatment in diseases requiring both chronic and acute care.]
5. What are true component costs of different dosage forms of medicines for children?

6. What might be effective strategies for implementing programs that introduce dispersible tablet/other new forms? E.g. zinc, cotrimoxazole experiences – including the importance of policy advocacy.
7. What can be done to standardize and inform on methods for the manipulation of authorized dosage forms (extemporaneous preparation versus manipulation prior to administration) in children?
8. What is the best method of providing information for health workers and carers, related to the optimal administration of medicines to children? E.g. pictograms, auditory messages.
9. What can be done to develop a micro-coating that is absorbable, dissolvable, and immune to degradation by chewing, and environmental or delivery-vehicle temperature changes?

Next steps and outstanding issues

The recommendations from this technical meeting will be published on the Expert Committee meeting website, reviewed by representatives from industry, academia and end-users in the public and private sector, and discussed at the next meeting of the Committee on Essential Medicines in March 2009. The literature reviews will be further developed and submitted for publication. Additional information will be sought from other potential resources such as the food industry and the 'over the counter medicine' industry, who may be able to provide relevant input on aspects in the development of pediatric dosage forms such as palatability and patient preference.

Promotion of the need for the preferred dosage forms is required. Pharmaceutical companies interested in the manufacture of these dosage forms need to be identified. Health care workers and carers of children need to expect 'preferred dosage forms'.

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

It is acknowledged that recommendations currently being presented are not fixed, and that depending on the degree and speed of further technological development, they will probably require revision in subsequent years.



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Annex 1

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