

Consultative meeting of an informal working group on extemporaneous formulations of medicines for children

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This publication contains the report of a Consultative meeting of an informal working group on extemporaneous formulations of medicines for children and does not necessarily represent the decisions or policies of the World Health Organization or UNICEF

Background

An informal working group on extemporaneous formulations for children has been meeting by teleconference since August 2009. The opportunity for a face-to-face meeting was provided by the World Pharma 2010 Congress which took place in Copenhagen, Denmark July 18-23. Ms Atieno Ojoo of UNICEF Copenhagen convened the working group and some additional resource persons at a meeting on July 20. The agenda provided an opportunity to review progress over the past year and to formalize an action plan going forward.

Attendees were welcomed to UNICEF by Bernadette O'Brien, Contracts Manager, essential medicines UNICEF SD.

Sue Hill: WHO perspective

The discussions at the core of this meeting have their origins in the World Health Assembly resolution of 2007 supporting better medicines for children. A key component of the Make Medicines Child Size program is the development of more appropriate formulations for young children and for those living in low resource settings. In December 2008, WHO convened an initial meeting to evaluate dosage forms of medicines. For children¹ Discussions from that meeting were carried further at a meeting in Accra, Ghana in August 2009.² Dr Hill reviewed this history and emphasized the importance of efforts to develop suitable dosage forms of medicines for children, and also to further secure optimal access and supply. It was noted that for some products it is unlikely that there ever will be child-specific products because the market is too small.

Discussions in the working group to date have focused in several areas:

- The need to define dosage forms of medicines that are currently available.
- Identification of characteristics of ideal dosage forms for children; liquids vs dispersible tablets, fixed dosage vs flexible dosage forms.
- The need for validation and standardization of relevant supporting information.

Current funding for the work on Medicines for Children is already committed and does not cover some additional activities required to address these areas that have been proposed.

The current ad hoc working group agreed to look at the present situation relating to extemporaneous preparations and manipulation of commercially available products. There is agreement in principle that action is required and that preferably, this should lead to a WHO guideline on permissible product manipulation. However, development of a WHO guideline would require complying with WHO guideline processes, including the compilation of existing evidence and information as a first step.

¹ http://www.who.int/childmedicines/progress/Dosage_form_reportDEC2008.pdf

² http://www.who.int/childmedicines/progress/Accra_final.pdf

There are some important information sources that could contribute to this activity, including the CPA survey described below. This survey will document what is actually happening in African real world settings. The survey and parallel information compiled by David Woods could help with progress towards a WHO pediatric formulations guideline that might be added to the WHO model formulary for children (WHO MFC).

The degree of detail likely to be required is potentially problematic. For example, the specifications for water used to make extemporaneous preparations may not be practical outside developed countries. It is recognized that there will be a challenge in finding funding to support work on formulations (see below).

David Woods: Expert advice on extemporaneous preparations

David Woods has been working on a database of products available for children since the 1980s. His guidelines have been made available on the internet free of charge.³ An important feature of the website is an educational component with question/answer capability. The answers to about 700 questions are included on the record. The project receives no funding and the current database needs to be updated. It does have the potential to be further developed with a strong educational aspect added.

Generally speaking world literature is not helpful to practitioners in developing countries since 90% of published studies involving extemporaneous preparations used formulations that included relatively expensive commercial suspending agents (e.g., Ora-Plus, Ora-Sweet). It would be more helpful if such studies included parallel testing of simpler formulations, using readily available and inexpensive suspending agents, such as methylcellulose.

David Woods emphasized the importance of the educational component to any future program. All alternative products should be considered before a decision is made to use an extemporaneous preparation. It is clear that guidelines or standards are needed laying out the choices to be made between therapeutic products and different commercial pharmaceutical preparations.

He noted that, in some countries regulatory authorities urge pharmacists and physicians to prepare syrups from tablets rather than to buy more expensive commercially available liquid products.

The following steps were suggested to address the issue of extemporaneous preparations:

- Incorporation of educational standards in the form of an externally validated guide sanctioned by an international authority, such as WHO. (Note: the guide should cover general principles of medicinal preparation, as well as including focused comments on high priority/high usage volume individual drugs.)
- Identification of the most important drugs is feasible and should not total more than 100. Priorities could be decided on the basis of data forthcoming from the CPA survey.

³ <http://www.pharminfotech.co.nz/>

- The knowledge transfer component is very important. An interactive Q&A database should be made available as an educational tool.
- An accompanying knowledge transfer strategy should also address the need to inform practitioners about alternative approaches, especially those most readily adopted for practice in low resource settings.

In discussion it was suggested that companies providing flexible suspending agents should be approached once it has been decided that a limited range of extemporaneous suspension agents is indeed appropriate. It was felt that it should be possible to gain recognition of universal suspension vehicles with defined specifications. In this situation there would probably be generic manufacture and more attractive pricing.

It was suggested that there are generic suspending agents already available (e.g., in India). It was noted that there are also existing groups who have accumulated specifications on pediatric formulations (e.g., Compounding Interest Group {CIG} in the UK and E-Drug, an on-line discussion group that specifically targets health workers in developing countries). Any advice that is eventually endorsed must be evidence-based.

The working group concluded that it would be possible to develop a document in this area. The final product could be a guidance prepared cooperatively between WHO and international organizations such as FIP and CPA. It was estimated that such a project might be completed in about 18 months for a budget of US\$250K. An alternative approach would be to add information to the new WHO MFC as an annex targeted to provide guidance on preparations.

A third option which was favoured by the working group was preparation of a discussion paper for the next meeting on the Expert Committee on Selection and Use of Essential Medicines. If this is to be pursued, Tony Nunn and David Woods would produce a general guidance document for circulation to the working group. Once edited the general guidance could be posted in November 2010 and discussed by the Expert Committee at its meeting in March 2011. The suggested title for the general guidance would be "A basic guide to providing pediatric options for formulations". The guidance would include alternatives, options for dealing with dosage forms at the point of administration, and options for extemporaneous preparation. The document to be produced should be oriented toward low and middle income countries but not exclusively so.

Dr Hill indicated that WHO may be able to identify modest funding to support the development of such a working paper for discussion in the September-November period and posting in November.

John Farwell: Extemporaneous preparations in developing countries

After discussions at the CPA meeting in Accra CPA agreed to carry out a survey in African Commonwealth countries concerning the use and preparation of extemporaneous products. Using the internet and names of individuals with pediatric pharmacy interests obtained through CPA, a total of 80 individuals in 15 countries were asked to participate. Another 25 names from Nigeria have recently been received and they will also receive invitations. So far 32 individuals have responded from 13 countries and have agreed to participate. It is anticipated that these numbers will increase further in the next few weeks.

The initial questionnaire is straightforward:

1. extemporaneous preparations used on a regular basis
2. extemporaneous preparations used occasionally
3. identification of products needed but not available or with obstacles to use (e.g., sustained release tablets)

A second questionnaire will seek more specific information related to selected products and individual preparations being used. Details of preparation procedures will be sought, as well as operational policies in place to cover preparation methodologies. Questions will be included about preparation facilities, staffing, and quality control. Based on survey responses some products will be identified for further development work and for potential encouragement of future commercial development. Standard protocols for testing in the field may also emerge from this survey.

It is anticipated that the survey will show that in some cases products are being manufactured locally as a cost saving measure. It was suggested that once the survey is completed in Africa, consideration should be given to expanding to other Commonwealth countries and to South America.

All members of the working group agreed that the survey should be pressed forward and eventually be rolled out to other continents. It is hoped that the initial results will be suitable for presentation at meetings in 2011 in Durban or Hyderabad.

Concern was expressed that in some countries commercial drug producers use 'right to information' legislation in order to identify situations in which extemporaneous preparation are being used. Once the information is obtained a protest is filed suggesting illegality of the product in the absence of proof of efficacy and licensing by a regulatory agency.

Dave Knoppert: Pilot projects

- Lexicomp
- Broselow tape

Dave Knoppert discussed two potential pilot studies that might be undertaken by the working group. He reported that he had had discussions with Lexicomp concerning possible pilot testing of their information service in five African hospitals with a view toward adapting information for developing country use. (Note: We were subsequently advised that Lexicomp information was one of the sources used in developing the WHO MFC) A problem with Lexicomp is the slow downloading speed in public hospital systems in Africa; securing high speed links may prove problematic.

It would be important to identify specific information needs and to adapt Lexicomp monographs for expanded use within the WHO MFC. The WHO MFC is available electronically free of charge and is likely to become a prime source of prescribing information for children.

The working group also discussed problems experienced in accessing the BNFc and the USP. It was noted that the BNF does provide the previous years' version free in hard copy; however, this program has not been extended to developing countries in spite of requests. Dr Batmanabane reported that she had succeeded in obtaining copies of the BNFc for use in India.

The WG also discussed the use of the system developed by Jim Broselow (University of Florida) to simplify drug dosing decisions for children using weight bands and proxies for weight. The Broselow system has been developed in North America and has not been adequately validated in developing countries, although there is some preliminary testing in African emergency rooms. It is anticipated that substantial revision will be required. Widespread use of the Broselow approach might eventually require considerable modification in available pharmaceutical preparations.

It was noted that Dr Charles Larson (University of British Columbia) has developed a protocol for validating a new system based on weight bands and weight proxies to be measured in rural Uganda and Bangladesh. It has been shown that in rural Uganda accurate weighing facilities are available in fewer than 20% of treatment sites. The estimated budget for such a validation study is \$200K. WHO has identified the validation of weight bands in different countries as an important priority but has encountered problems in gaining access to datasets that might be applied to this need. Anthropomorphic growth data is available in at least 8 countries but it has so far proven impossible to get it released for use in complementary analyses. If these databases were accessible answers could be quickly obtained. Pediatric academicians may need to push for resolution on this issue. Advocacy would include approaching agencies/departments within WHO to see if their data will be shared for this purpose.

It was suggested that a weight proxy system could be readily validated for African use in Botswana using the data on 10,000 children available from the Baylor/University of Botswana HIV treatment program. The dataset includes information on many children investigated but later proven to be deemed disease free.

Funding challenges

While the fundamental importance of formulation and dosing guidance issues is well recognized in child health care in developing countries, it has nonetheless been difficult to mobilize resources to support the research necessary to bring about improvements. New revenue sources should be sought from outside WHO and UNICEF. In some cases, such as validation of the Broselow tapes, project specific funding should be sought. Potential funding sources were discussed, including:

- ELMA Fund
- Children's Investment Foundation Fund CIFF
- Thrasher Foundation
- UNITAID
- European Community FP7
- BMGF
- International Development Research Centre (Canada)

Dr Hill agreed to discuss the identified needs at the forthcoming partners meeting to be held mid-October in Geneva for the Better Medicines for Children project. It was noted that any funding requested from UNITAID would need to be linked to a specific objective such as development of a universal suspension vehicle for application in treatment of HIV, malaria, and TB. It was suggested that there may be funds available in the UNICEF 'Innovate for Children' program.

All members of the WG agreed that considerable progress could be achieved with modest resources, including completion of the CPA survey, revision and updating of drug information materials, and validation of the Broselow tape or other weight proxies using existing well-documented study cohorts (e.g., Baylor program, Botswana).

Action steps

- 1) Tony Nunn and David Woods agreed to complete preliminary work on a basic guide and discussion paper, including standardization of information packages.
- 2) Atieno Ojoo and Dave Knoppert will circulate the discussion paper for review by the working group in October/November.
- 3) If a final version is agreed, it will be posted in November for consideration by the Expert Committee at its meeting in March 2011.
- 4) John Farwell will complete the CPA survey amongst participating African countries and will consider extension of the survey to India and South America, perhaps using the FIP network (liaison: Andy Gray). A report will be prepared for further discussion and dissemination. (timeline: December 31, 2010) The report will also be presented at the CPA Conference in Durban in May 2011.
- 5) Best efforts will be made to obtain validated weight proxies from Africa and India to support the dissemination of a weight band dosing guide suitable for use in developing country populations. Stuart MacLeod will seek funding support for this project and will explore means of accessing existing data cohorts within WHO and from other sources.
- 6) Efforts to obtain adequate resources for support of the dosing guideline aspects of this workplan will be made by Sue Hill, Greg Kearns, and Stuart MacLeod. Drs Kearns and MacLeod will contact competitive funding agencies with potential interest in the practical projects outlined.

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Agenda

- 0830-0900:** Introductions, opening remarks and WHO update on number 2 above(In context of the bigger project, recap of priority areas for 2010-2012)
Sue Hill
- 0900-0930:** Expert advice on extemporaneous preparations: How to put together a package of standards, methods, and technical skills
David Woods
- 0930-0945:** Extemporaneous preparations in developing countries: Gap analysis and priority products update(CPA work)
Tony Nunn
- 0945-1015:** Coffee break 30 minutes
- 1015-1030:** Lexicomp pilot project proposal
Dave Knoppert
- 1030-1200:** Round table discussion: Developing standardized approaches to extemp preps. Facilitated by **Sue Hill and Tony Nunn**
- a. What? Based on expert advice from David Woods
 - b. Roles and responsibilities moving forward
 - c. Proposal for Funding?
 - d. When? Timelines?
- 1200-1215:** Summary-next steps
- 1215-1300:** Tour of the UNICEF warehouse (Optional)

List of participants

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