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http://dx.doi.org/10.1016/j.ijpharm.2012.05.053

WHO guideline development of paediatric medicines: Points to consider in pharmaceutical development

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World Health Organization (WHO) guidance on the pharmaceutical development of paediatric medicines is being developed in the form of a "points to consider" document by the WHO Expert Committee on Specifications for Pharmaceutical Products. The current draft (Working Document QAS/08.257/Rev.3) will be submitted for adoption to the Expert Committee at its meeting in October 2011 and, hopefully, for final endorsement by the WHO Governing Bodies early next year and, hence, recommendation to Member States and other parties for implementation.

WHO launched in December 2007 its initiative "Make Medicines Child Size" in order to raise awareness and accelerate action to the need for improved availability and access to child-specific medicines. The WHO Model Formulary for Children 2010 provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO Model List of Essential Medicines for Children, first developed in 2007 and reviewed and updated every second year.

The current "points to consider" document is another result of the efforts. The scope of the document is to present information to manufacturers and regulatory authorities on issues that require special attention in the pharmaceutical development of paediatric medicines, including also for use in developing countries. Such information cannot be exhaustive and will need updating along with progresses in our knowledge about development and uses of paediatric medicines. In parallel with this guidance, the Expert Committee has also developed a guideline on the pharmaceutical development of multisource (generic) products (Working Document QAS/08.251/Rev.3).

Table 1
Some desirable features of paediatric dosage forms (WHO Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. December 2008).

◯ Convenient, reliable administration
◯ Preferably ready-to-use formulations
◯ Minimal manipulation by health care professionals, parents or caregivers
◯ Dose and dose volume/weight adjusted to the intended age group
◯ Acceptable and palatable dosage form
◯ Minimum dosing frequency
◯ Minimal impact on life style
◯ Minimum, non-toxic excipients
◯ Transportable and low bulk/weight
◯ Easy to produce and stable in as variety of climates
◯ Affordable
◯ Commercially viable

Table 1 lists some of desirable features of paediatric dosage forms. Some of these are common to all paediatric medicines, while others address end-user needs in developing countries.

It is important to bear in mind supply chain considerations such as ease of transportation and storage requirements. For example, storage in a refrigerator is not always possible. Lack of access to clean water is an important issue to take into consideration in the development of medicines to be dissolved, diluted or dispersed prior to administration. Regional and cultural differences with regard to preferred taste need to be considered as well as cultural differences in the use of and expectations to a medicine.

Dosage forms that, in general, are likely to prove most suitable, including also for developing countries, and which should be prioritized, are flexible dosage forms such as sachets and tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups. It is believed that the flexible dosage form design may be used for various active ingredients (APIs) provided that they do not require a precise dose titration or not belonging to the poorly soluble BCS classes. If the medicine can be dispersed in breast milk from the mother, it could potentially be used in very young children (less than 6 months).

For medicines that require precise dose measurement or titration, suitable dosage forms could be based on a platform technology to produce multiparticulate solids such as minitablets and spherical granules/pellets that allow production of dosage forms of varying strength as well as different dosage forms like tablets and capsules, and also dosage forms to be dispersed to form a liquid dose or sprinkled onto food. Platform technology has a potential flexibility for constructing appropriate fixed dose combination products (FDCs).

The WHO recommendation of such solid forms should also be seen in the context of product stability (generally no need for stabilizing agents), production using standard equipment, ease of transportation and low bulk volume/weight.

The WHO guidance document recognizes of course that various routes of administration and dosage forms are considered for the paediatric population. It provides *pro et contra's* for their formulation and use in the paediatric population. Emphasis is given to formulations for oral use, rectal use, parenteral administration, dermal and transdermal administration and inhalation use.

The choice of excipients and their level in dosage forms is a major challenge for the formulation scientist. The use of excipients is driven by functional requirements and should be justified through a risk based assessment taking into account amongst others the factors listed in Table 2.

The added challenge for paediatric medicines compared to adult medicines is that excipients in children may lead to adverse reactions that are not experienced in adult medicines or not seen to the same extent. Reviews on adverse reactions attributed to excipients show however that currently available data of excipient safety are of limited quantity and variable quality. Thus, it is not possible to day to outline specific recommendations

Table 2
Factors to consider in the choice of excipients.

- Safety profile of the excipient for children of the intended age group(s)
- Route of administration
- Single and daily dose of the excipient
- Duration of the treatment
- Acceptability for the intended paediatric population
- Potential alternatives
- Regulatory status in the intended market

for the choice of excipients. In the formulation of paediatric medicines, the number of excipients and their level in a formulation should be the minimum required to ensure an appropriate product with respect to performance, stability, palatability, microbial control, dose uniformity and other considerations to support quality.

Potential alternatives to excipients posing a significant risk should always be considered. Another formulation or even route of administration might be necessary to avoid significant risk. In addition, alternative excipients may need to be considered because of different cultural or religious reasons, e.g. the use of gelatin may not be acceptable for all patients.

General guidance regarding safety of some types of excipients are included in the "points to consider" document, namely coloring agents, antimicrobial preservatives, sweetening agents, taste masking agents and solubility enhancers.

Quality attributes of paediatric medicines do not differ from those of adult medicines. The WHO guidance document makes therefore reference to current quality guidelines and pharmacopoeias, for example ICH guidelines on the acceptable level of impurities in APIs and degradation products in finished dosage forms. The WHO's experts' viewpoint is that safety margins established during toxicological studies apply to both adults and children; although a child would receive a lesser dose, the exposure per kg is likely to be similar. Term and pre-term neonates have however to be considered specifically. With regard to dissolution testing, dissolution media prescribed or recommended in pharmacopoeias should be carefully re-considered in view of the different gastric pH of the child.

Container-closure systems for paediatric medicines are designed and constructed of materials meeting relevant regulatory requirements and taking into account the stability of the medicines during storage, transport and use. In addition, they are designed with a view to accurate dosing and convenient administration, robust and convenient for the supply chain and tailored to the target age group. The packaging should provide information on the use of the medicine as adequate information about the medicine and its use, are highly important. Drawings or pictograms showing time, method and route of administration are strongly recommended. In cases where the paediatric medicine is significantly different from a similar adult medicine, it would be important to have the product packaging be noticeably different between the two products.

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http://dx.doi.org/10.1016/j.ijpharm.2012.05.054

International initiatives on extemporaneous dispensing☆

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Extemporaneous compounding is important to paediatric practice to allow the provision of age-appropriate dosage forms when appropriate authorised medicines are not available. In resource-poor countries even common medicines such as oral paracetamol liquid may be compounded because access to priority medicines from the WHO Essential Medicines List for children is not assured. The process of compounding is not without danger and there may be alternative strategies such as dose-rounding, therapeutic substitution or manipulation of 'adult' dosage forms so that compounding is a last resort. WHO has commissioned literature review and guidance to better inform practitioners on the risks and the alternatives. The preparation of the guidance is briefly reviewed and recommendations for further action are presented.

Extemporaneous dispensing or compounding is considered an important practice by paediatric pharmacists in Europe and North America which enables the provision of age-appropriate formulations (often oral liquids) when no authorised preparation is available. Pharmaceutical manufacturers have an interest in the practice to substitute for manufactured products in clinical trials or when manufacturing is difficult or costly. Regulators have concerns about the quality of product produced by extemporaneous dispensing and with bioavailability. There are few standards for extemporaneous dispensing in European countries but, with a recent resolution, the European Council will seek to avoid quality and safety gaps between medicinal products prepared in pharmacies and those prepared on an industrial scale (Committee of Ministers, 2011).

Many resource-poor countries will use the World Health Organization (WHO) Essential Medicines List for children as the starting point for a national list of medicines to be made available. Additional information on the drugs, doses and dosage forms is provided in the WHO Model Formulary for Children (WHO, 2010) but not all age-appropriate dosage forms are listed and many will only be available in certain countries. Little is known about extemporaneous dispensing in resource-poor countries but there is evidence of lack of access to many essential medicines especially age-appropriate preparations for children (Robertson et al., 2009). 70% of 475 information requests concerning compounded preparations concerned medicines available in other markets with Quinine, prednisone and rifampin the most frequently requested specific drugs (Woods, 2010). A meeting of WHO representatives from Anglophone African countries identified extemporaneous dispens-

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