Progress made in the Medicines Quality Assurance Programme
For "Better Medicines for Children"

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Contribute to WHA60.20

Developing norms, standards and guidelines to promote better medicines for children through the WHO Expert Committee on Specifications for Pharmaceutical Preparations
## Progress Made: 2007-2011

<table>
<thead>
<tr>
<th>Guideline development</th>
<th>Other activities</th>
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</thead>
</table>
| ▪ Development of paediatric medicines: points to consider in formulation | ▪ Monograph development  
  ▪ Monographs for paediatric medicines  
  ▪ Paediatric approached work plan  
  ▪ Regulatory advice: First meeting of the Paediatric Medicines Regulators' Network, 2010  
  ▪ Paediatric medicines in the WHO Prequalification of Medicines Programme |
Scope of the document

To inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical development of paediatric medicines.

- Not to detail instructions, rather to make reference to relevant literature
- Formulation and dosage forms
History of the document

- First draft: 2007
- New draft: 2008
- 42nd Expert Committee meeting
- 2009
- Coordination with other ongoing activities both within and outside WHO
- Discussion at informal consultations in 2008 (2), 2010, 2011
- Circulation for comments, inputs and feedback
- Presentation to Expert Committee meetings: 43rd, 45th, 46th
- 2010
- 46th Expert Committee meeting
- Adopted 2011
Contents

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3. Dosage forms to be considered in particular
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Dosage forms selection principle

The guiding principle for selecting paediatric dosage forms should be – as for adults – the balance of risk/benefit, taking into account the specific needs of this vulnerable population.
# Dosage forms selection principle

<table>
<thead>
<tr>
<th>Convenient, reliable administration</th>
<th>Acceptability &amp; palatability</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dose volume or size appropriate for the target age group/accurate dosing requirements</td>
<td>- Acceptability in dosage form, dosing device, dose volume/size, packaging, and clear and accurate labelling, etc.</td>
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<tr>
<td>- Dose manipulation should be kept to a minimum level</td>
<td>- Palatability in itself without any need for further modifications</td>
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</table>

<table>
<thead>
<tr>
<th>Minimum dosing frequency</th>
<th>End-user needs</th>
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<tbody>
<tr>
<td>Facilitate compliance to dosing scheme for both caregivers and older children</td>
<td>- Convenient to produce and affordable</td>
</tr>
<tr>
<td></td>
<td>- Restrictions on the applicable dose volume/size – minimum to be attempted</td>
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<tr>
<td></td>
<td>- Supply chain considerations, e.g. ease of transportation, storage requirements</td>
</tr>
<tr>
<td></td>
<td>- Access to clean water</td>
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<td></td>
<td>- Adequate product information</td>
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</table>
Dosage forms to be considered in particular

Flexible solid dosage form is the most suitable dosage form

- A dosage form that can be administered to patients in more than one manner, e.g. taken orally as a whole or to be dispersed or dissolved prior to administration.
  - e.g. orodispersible tablets, dispersible tablets, soluble tablets

Consider platform technology if precise dose measurement or titration is needed

- Technology, including formulation and related processes, that can be used to obtain different dosage forms, different strengths and/or accommodate different APIs.
  - produce multiparticulate solids, e.g. pellets, minitablets
# Dosage forms to be considered in particular

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Key advantage</th>
<th>Key consideration</th>
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</table>
| Flexible solid dosage forms | - Suitable for both developed and developing countries  
- Can be used for preparation of oral liquids suitable for very young children: <6 months  
- May be used for various APIs | Not suitable for medicines requiring a precise dose titration  
Compatibility of API and breast milk needs study |
| Requiring precise dose measurement - oral medicines | Suitable for precise dose measurement or titration | Platform technology |
| Parenteral formulations | For severe disease conditions | Requiring a trained caregiver to use |
| Rectal preparations | Severely ill children or children unable to swallow | Cultural barriers to use |
Formulation design

- Quality
  - Biopharmaceutics Classification System (BCS)
- Colouring agents
  - Antimicrobial preservatives
- Taste making
  - Solubility enhancers
- Excipients
  - Sweetening agents
Excipients

- Use of excipients is driven by functional requirements and should be justified through a risk-based assessment, taking into account the paediatric age group, frequency of dosing, duration of treatment, etc.
- Should be minimum required number and their level in a formulation.
- Excipients may lead to adverse reactions not experienced, or not seen to the same extent, in adults. Adverse reactions are mostly associated with excipients used for liquid dosage forms.
- Well-known excipients with a well-defined safety profile to be preferred.
- Only use novel excipients when safety, quality and appropriateness of use in children have been established.
Route of administration

- Oral administration
- Rectal administration
- Parenteral administration
- Dermal and transdermal administration
- Inhalations
Packaging and Labelling

- Container-closure systems are designed and constructed of materials meeting relevant regulatory requirements and taking into account the stability of the medicine during transport, storage and use.
- In cases where the paediatric medicine is significantly different from a similar adult medicine, the product packaging should be noticeably different between the two products.
- Facilitate safe self-administration of medicine in school children and adolescents.
- Adequate information about the medicine and its use; specific instructions about how to measure and administer a precise dose.
- Strongly recommend drawings or pictograms showing time, method and route of administration.
Coordination

The preparatory work has involved coordination with other ongoing activities, both within and outside WHO, especially with the European Medicines Agency, the United Nations Children's Fund, the WHO Model List of Essential Medicines and the Essential Medicines project.

- Reflection Paper: Formulations of Choice for the Paediatric population (2006), European Medicines Agency (EMA)
- First draft
Paediatric medicines development is limited in some areas (e.g. acceptability of dosage forms, safety of excipients), but it is also a rapidly developing field. An update of the document might be needed in the not too distant future.
References: guideline

2. WHO guideline on quality risk management (working document QAS/10.376).
4. Pharmaceutical development for multisource (generic) pharmaceutical products (working document QAS/08.251/Rev.1).
5. Impurities in New Drug Substances, ICH Topic Q3A(R2).
6. Impurities in New Drug Products, ICH Topic Q3B.
7. Impurities: Guideline for Residual Solvents, ICH Topic Q3C.
10. Specification Limits of Residues of Metal Catalysts (CPMP/SWP/QWP/4446/00).
References: literature


References: literature (continued)


