

# **PRIORITY MEDICINES FOR CHILDREN 2013**

**ACHIEVEMENTS SINCE 2004  
AND AREAS FOR IMPROVEMENTS**

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# **PRESENTATION CONTENT**

## **MEDICINES FOR CHILDREN**

- The Paediatric Knowledge Gap
- Paediatric populations specifics and Disease patterns
- Formulation Considerations
- Regulatory aspects
- Achievements and remaining gaps
- Conclusions




# PAEDIATRIC KNOWLEDGE GAP

## Children - “not small adults”

- ➔ Vulnerable population with developmental, physiological and psychological differences between age groups and from adults
- ➔ Paediatric dosage regimens cannot be simply extrapolated from adult data

## Children - “Therapeutic orphans”

- ➔ Majority of marketed medicines not studied in children or approved for paediatric use (only **1/3** of all EMA medicines authorised 1995-2005 are licensed in children)  
Ethical. economic, logistical and technical barriers for CT
  - ➔ Risks: adverse effects (overdosing), inefficacy (underdosing), improper formulations, delay in access to innovative medicines
- 

# Paediatric specific diseases and patterns

- Epilepsy
  - Cancer
  - Rheumatoid disease
  - Atopic Diseases
  - Respiratory distress
  - Congenital abnormalities
- 
- ➔ Diagnosis, prevention and treatment of these conditions have to be investigated in children
  - ➔ Safe / effective treatments for adults may be dangerous / ineffective for children
  - ➔ Effective treatment at early stage of the disease may be beneficial



# APPROPRIATE PAEDIATRIC FORMULATIONS

Purpose of good paediatric formulations is to achieve safe and accurate dose administration, reduce the risk of medication errors, and enhance the compliance with medications.

## Basic criteria for paediatric drug formulations:

- Sufficient bioavailability
- Safe excipients
- Palatable and/or acceptable properties
- Acceptable dose uniformity
- Easy and safe administration
- Socio-cultural acceptability
- Precise and clear product information

*Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Exp Opin Drug Deliv 2007; 4:37–45*

Technical challenges, such as: diversity of children, accuracy of dosing with lower paediatric doses and volumes, inability to swallow solid dosage forms, taste masking in oral forms, stability, unsafe excipients, needlephobia and small veins for parenteral forms



# Suitability of routes and formulations

Route	Dosage Form	Preterm newborn infants	Term newborn infants (0d-28d)	Infants and Toddlers (1m-2y)	Children (pre school) (2-5y)	Children (school) (6-11y)	Adolescents (12-16/18y)
<b>Peroral</b>							
	Solution/ Drops						
	Emulsion/ Suspension						
	Effervescent DF*						
	Powders/ Multiparticulates						
	Tablets						
	Capsules						
	Orodispersable DF						
	Chewable tablets						
<b>Nasal</b>							
	Solution						
	Semisolid DF						
<b>Rectal</b>							
	Suppositories						
	Rectal Enema						
	Rectal capsules						

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

WHO Headquarters, Geneva, Switzerland

15-16 December 2008



make medicines **child size**

## 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.

# Dispersible tablets



**Fig. 2** Multifunctional tablet for paediatric use: Coartem® (Novartis). The tablet can be dissolved in glass or a small volume of liquid on a spoon prior to administration. The formulation is specifically designed for malaria treatment of children in developing countries with high temperatures and humidity



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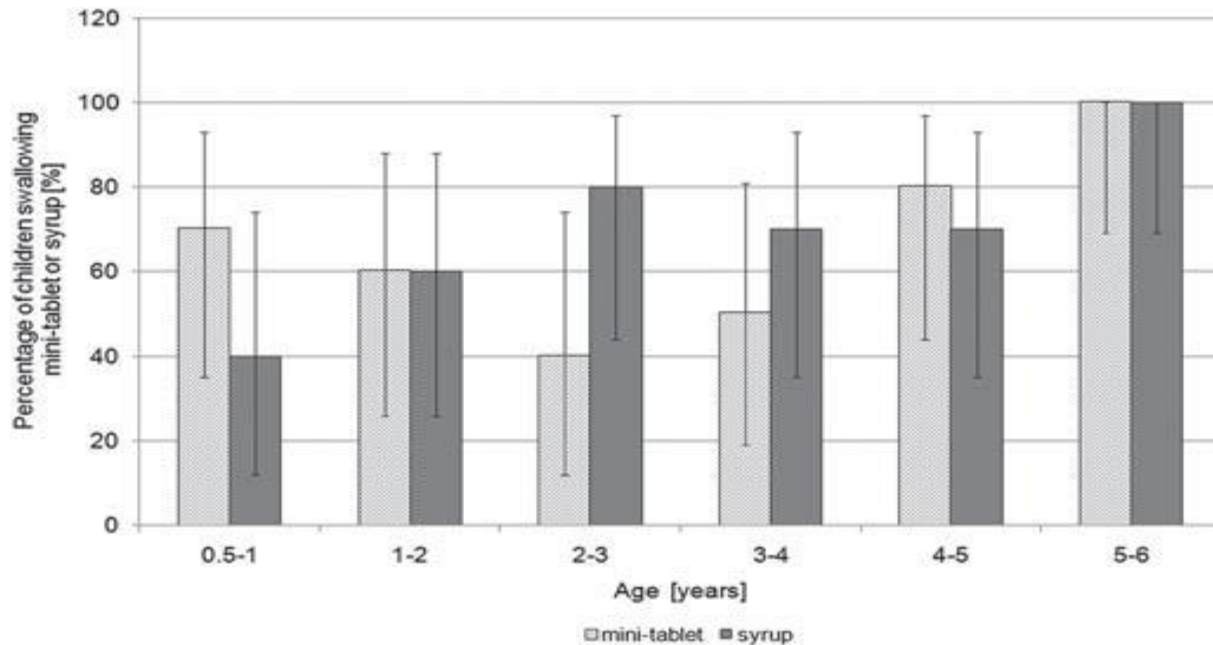


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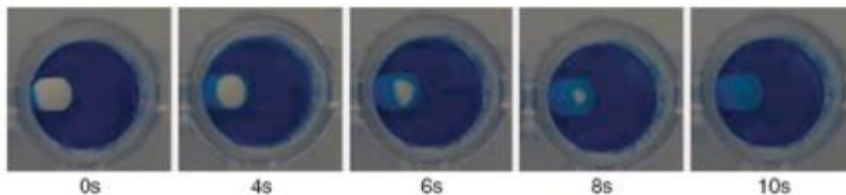
3. For oral medicines requiring precise dose measurement or titration, the most 'suitable' dosage form should be based on use of a solid platform technology (multi particulate solid, including those that could be dispersed to form a liquid dose), rather than oral liquids. This can allow production of '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.

SPOMER N, KLINGMANN , STOLTENBERG I, ET AL. ACCEPTANCE OF UNCOATED MINI-TABLETS IN YOUNG CHILDREN: RESULTS FROM A PROSPECTIVE EXPLORATORY CROSS-OVER STUDY. ARCH DIS CHILD 2012;97:283–286.

STOLTENBERG I, BREITKREUTZ J. ORALLY DISINTEGRATING MINI-TABLETS (ODMTs) – A NOVEL SOLID ORAL DOSAGE FORM FOR PAEDIATRIC USE EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS 78 (2011) 462–469



## Orodispersible mini-tablets



# INNOVATIVE FORMULATIONS AND DEVICES

## Granules / Sprinkles / Pellets



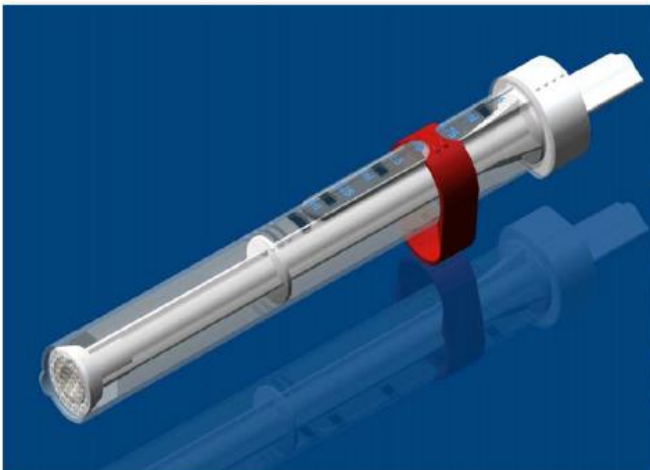
## Minitablets



Pankreatan (Novartis)  
Cholspasminase (Merck)  
Enzym-Lefax (Bayer)  
Cotazym (UCB)



Examples for different marketed orodispersible films and packaging variants.



inn, A. Breitenbach, J. Breitzkreutz, *Exp. Opin. Drug Deliv.* (2011)

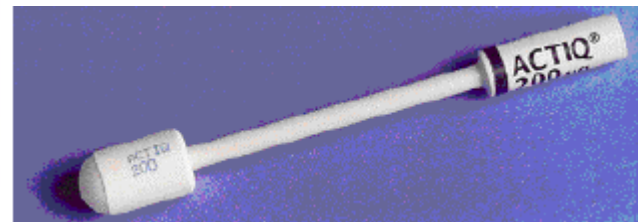


Fig. 4. Dose sipping syringe design (left) and child taking its medicine with the dose sipping syringe (right).

VAN RIET-NALES DA, SCHOBEN AF, EGBERTS TC, RADEMAKER CM. EFFECTS OF THE PHARMACEUTICAL TECHNOLOGIC ASPECTS OF ORAL PEDIATRIC DRUGS ON PATIENT-RELATED OUTCOMES. CLIN THER. 2010 MAY;32(5):924-38

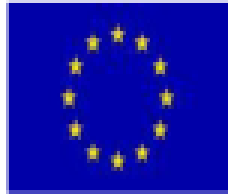
Table II. Impact of pharmaceutical technologic aspects on patient-related outcomes parameters.<sup>24-28,31-119</sup>  
Data are number (%) of assessments.

Patient-Related Outcomes Parameter	Pharmaceutical Technologic Aspect			All Assessments (N = 176)*
	Formulation and Dosage Form (n = 85)	Route and Frequency of Administration (n = 77)	Packaging, Administration Device, and User Instruction (n = 14)	
Patient acceptance	38 (45)	5 (6)	1 (7)	44 (25)
Patient preference	19 (22)	4 (5)	0	23 (13)
Adherence	11 (13)	15 (19)	6 (43)	32 (18)
Clinical efficacy	8 (9)	31 (40)	2 (14)	41 (23)
Side effects and tolerability	8 (9)	22 (29)	0	30 (17)
Administration errors	1 (1)	0	5 (36)	6 (3)

\*Two investigations assessed >1 pharmaceutical technologic aspect.

Review of effects of pharm technologic aspects (formulation and dosage form; route and frequency of administration; and packaging, administration device, and user instruction) on patient-related outcomes (clinical efficacy, side effects and tolerability, patient preference, patient acceptance, administration errors, and adherence).

- limited clinical evidence to support pharmaceutical development programmes (side effects/tolerability and administration errors with no attention)
- Poor methodologic quality, need for proper instruments to measure methodological quality (RCT/double blinding not appropriate)
- .Agreement on taxonomy of technological aspects and patient-related outcomes
- Creation of global database with literature on the development of pediatric pharmaceuticals to promote research in the neglected areas.



EU regulation „Medicinal Products for Paediatric Use“  
(enforcement: 26.01.2007)

**Paediatric Committee (PDCO)**

**Paediatric Investigation Plan (PIP)**

New chemical entities:

**Supplementary Protection Certificate (SPC)**

= Market exclusivity + 6 months

+ 24 months for orphan diseases

„Old“ drug substances:

**Paediatric Use Marketing Authorisation (PUMA)**

new type of marketing license:

exclusivity of study results: 10 years





# OFF LABEL AND UNLICENSED USE

2010 EU survey on 20 EU and 2 non-EU countries:

45-60% of all medicines in children used outside MA

Discrepancies across individual countries in unapproved medicines use due to differences in data collection methods, prescribing habits and medicines regulatory status (approved or not, in all or some subsets).

Make approved products available in all Member States through the Mutual Recognition and Decentralised Procedures address the general lack of paediatric labelling in the SPC, foster harmonisation of information on the product labels

## **Therapeutic classes most frequently used as off label and unlicensed medicines in the EU**

**Antiarrhythmics**

**Antihypertensives (renin-angiotensin inhibitors, beta blockers)**

**Proton pump inhibitors**

**H<sub>2</sub>-receptor antagonists**

**Antiasthmatics**

**Antidepressants (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants).**

**Antimicrobials (macrolides, beta lactam antibiotics plus beta-lactamase inhibitors, carbapenems)**

**Corticosteroids (dexamethasone)**

# DATA AVAILABILITY AND DISSEMINATION

- Paediatric medicines in the Netherlands  
<http://www.kinderformularium.nl/search/index.php>
- Patient information for unlicensed and off-label medicines specially prepared by pharmacists and doctors ([www.medicinesforchildren.org.uk](http://www.medicinesforchildren.org.uk)).
- BNFc, WHO Formulary



# ACHIEVEMENTS SINCE THE PAEDIATRIC REGULATION (1)

**Long-term impact:** strengthening infrastructure, setting norms and standards, building capacity for research and development of paediatric medicines, improved pharmaceutical quality of paediatric medicines (formulations/pharmaceutical forms)

**CT:** 350 trials/year (stable), number of trials in all populations declined 2007-2011, transparency (Eudra CT)

**PIP:** 70% proposed development of paediatric indications vs. 30% in the past, BUT, 25% of all agreed PIPs submitted exclusively for neonatology (highest need)

Therapeutic areas cover mostly diseases in adults (endocrinology/gynecology/fertility/metabolism, infectious diseases, oncology, cardiovascular diseases), not unmet/priority therapeutic paediatric needs (paediatric malignancies, pain, neonates).





## ACHIEVEMENTS SINCE THE PAEDIATRIC REGULATION (2)

- EU FP7 provides funding for 15 projects and 2 investigator-driven clinical trials for off patient medicines (75 mill. Euros).
- Centralized authorizations for paediatric use obtained for 34 new medicines, 38 new paediatric indications as variations of 33 already authorized medicines , 4 centrally authorized products had either a new pharmaceutical form, or a new route of administration, or a new strength authorized for paediatric use.
- Rewards obtained for 12 medicines:  
SPC extensions for 11 medicines, 1 PUMA exclusivity for the Midazolam paediatric oromucosal form).



# MAJOR GAPS AND CONSIDERATIONS RELATED TO EC REGULATION

- PIP coverage for paediatric developments: more profit oriented, not matching public health needs (adults therapeutic areas, older children groups preferred by industry)
- Priority needs list should not only be based on existing off label medicines use, but proactive approach based on real therapeutic advances and prioritising ;therapeutic areas of interest to children
- ADR of off patent medicines use in children: Healthcare professionals to help monitor the safety of medicines and report suspected adverse drug reactions.
- New EU Pharmacovigilance Regulation to cover both marketed and unlicensed/off label medicines in children.
- 1 PUMA granted, so PUMA not adequate incentive to the industry for off-patent drugs. This may be linked to reimbursement rules which may not recognize PUMA and may attach little values to old medicines even if they include a new age-appropriate formulation/form.
- Does PUMA granted product have therapeutic benefit over existing treatments?
- Midazolam has only minor therapeutic advances according to the French National Authority for Health (Prescrire)
- 6 months - SPC extensions example with Cozaar ( Losartan Potassium) oral suspension (MSD) in France
  - Losartan not standard treatment for hypertension in children
  - Suspension not ready to use, not labeled properly, poor quality packaging prone to dosing mistakes (diluting)
  - Medicine not available in pharmacies/wholesales and not included in the French reimbursement list, expensive, paid out-of-pocket, so unavailable and unaffordable
  - But, the manufacturer was given 6-month extension to its market exclusivity on Losartan in France, even for its non-paediatric indications

# DISCUSSION

Much progress done in the development of age-appropriate paediatric formulations, especially for oral route of administration.

Many innovative paediatric formulations and devices but few are available on the market, due to high costs (patents) and (un)willingness for refunds by health insurance bodies.

- Areas for future developments and research:
- New routes of administration such as oral-transmucosal (buccal strips), intra-nasal and trans-dermal (for neonates mainly).
- Children's ability to swallow and their preferences need to be investigated. This will direct future formulation research towards (mini) tablets, chewable tablets, dispersible tablets or more oral liquids.
- More research into alternative safe excipients for children such as natural polymers (e.g. cyclodextrin to mask taste of drugs, improve solubility or protect drugs/patient).



## CONCLUSIONS

- Regulations introduced for structured research in children and improved labelling
- Structured clinical research in children required to avoid harm
- Better data collection re: use of medicines and burden of diseases (chronic diseases) in the EU
- Pharmacovigilance and health system data to be used for efficacy and risks of off label medicine
- Data availability and dissemination

