NHS
National Institute for Health Research

EMA Workshop on Paediatric Formulations II
8 November 2011

Age-appropriate formulations – paediatric needs

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Requirement for dosage forms

- **Dose measurement**
  - Potency – mg/microgram/nanogram
  - Changes throughout childhood
- Protection
  - Humidity; oxygen
  - Gastric acid and enzymes
- **Conceal taste and smell**
- Liquid preparations of insoluble or unstable drugs
- Rate controlled action
- Optimise delivery
  - Topical
  - Inhalational
- Delivery direct to bloodstream or tissues
  - sterility

European regulation on medicinal products for paediatric use (26 January 2007)

- requires paediatric investigation plan (PIP) describing
  - measures to adapt the formulation to make it
    - more acceptable
    - easier
    - safer
    - more effective

  for different subsets of the paediatric population

What is an 'age-appropriate' formulation?

- Dosage form which
  - Can deliver variable doses (age/weight/SA related)
  - Delivers an accurate dose
  - Is safe and acceptable to the child
  - Is matched to development and ability
  - Avoids medication error

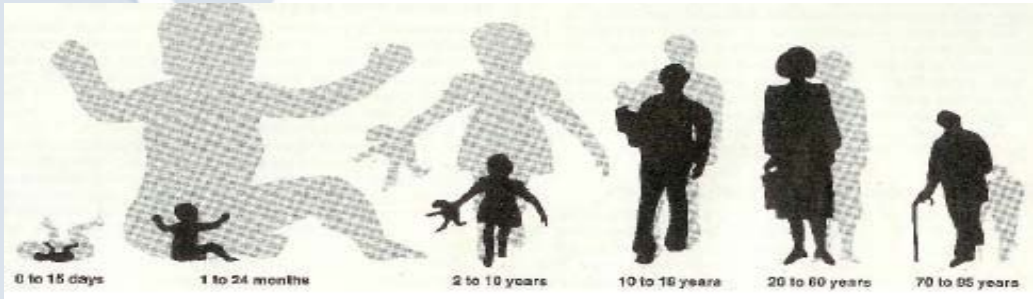
Ages and abilities

- Children v adults
  - Rapid growth, maturation and development
    - Developmental pharmacology
  - Change in magnitude of dose

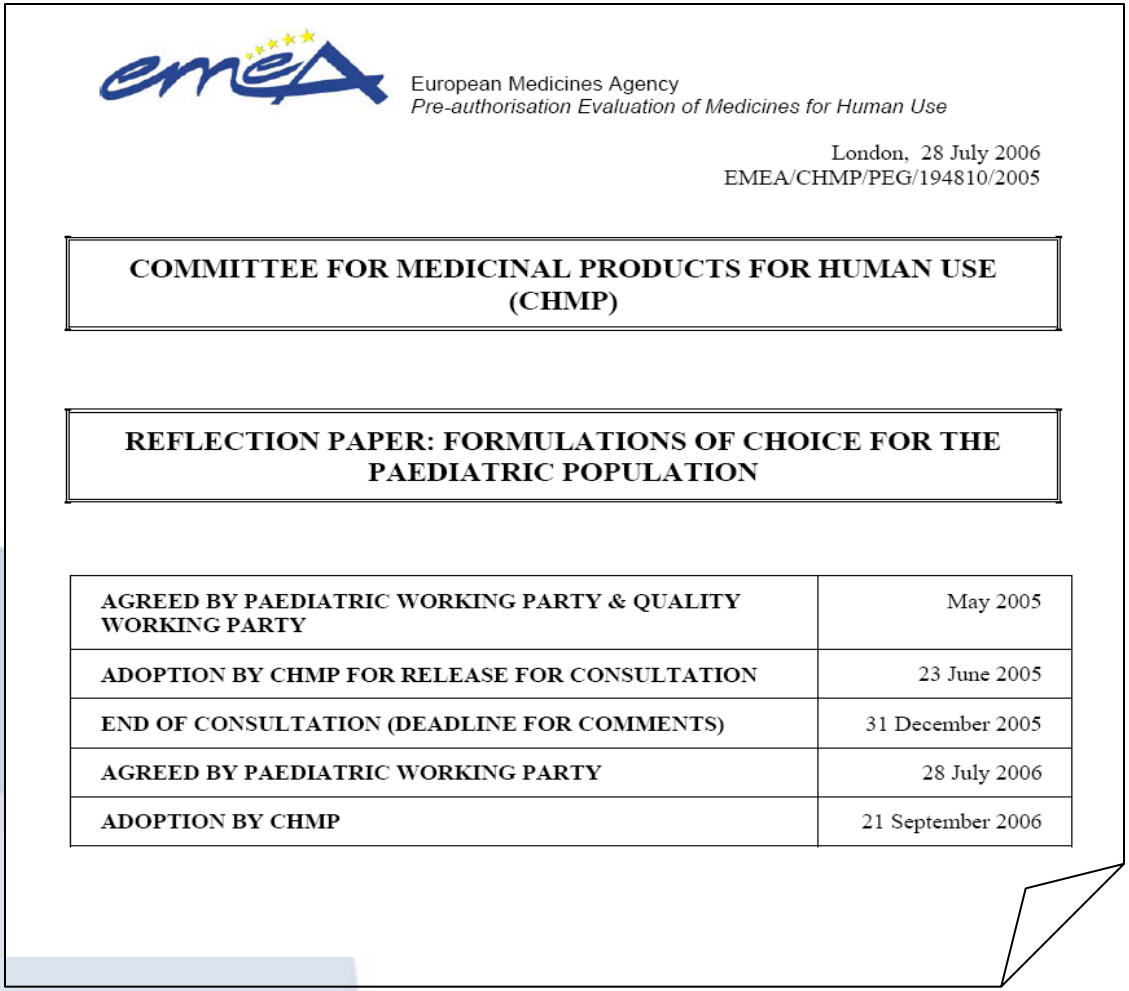
Baby	1 yr	6 yr	12 yr	adolescent
30-60 mg	120 mg	250 mg	500 mg	0.5-1 g

  - Change in ability to cope with dosage forms

baby	1 yr	6 yr	12 yr	adolescent
Drops (?)	liquid/'melt'	liq/'melt'/tab	tablet	tab/capsule



Reflection paper



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 28 July 2006
EMEA/CHMP/PEG/194810/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION

AGREED BY PAEDIATRIC WORKING PARTY & QUALITY WORKING PARTY	May 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 June 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 December 2005
AGREED BY PAEDIATRIC WORKING PARTY	28 July 2006
ADOPTION BY CHMP	21 September 2006

www.emea.eu.int/pdfs/human/peg/19481005en.pdf

PREFERRED DOSAGE FORMS

	PRETERM	TERM	INFANTS & TODDLERS	CHILD PRE-SCHOOL	CHILD SCHOOL	12-18
DROPS	++	++++	+++++	+++++	+++	++
LIQUID	++	++	+++++	+++++	+++	++
MULTI-PARTICULATE	+	++	++	++++	++++	+++++
TABLET	-	-	+	+++	++++	+++++
CHEW TABLET	-	-	+	+++	+++++	+++++
'MELT' TABLET	-	+	++++	++++	+++++	+++++

Factors to consider

in relation to the indicated target age groups. Depending on the aspects to be studied, the ICH classification groups for age may either be divided in smaller groups or combined.

In deciding on the appropriateness of the pharmaceutical design of a paediatric medicine, the focus of attention should normally be placed on:

- the minimum age of the target age group(s) and the relevant developmental physiology;
- the behavioural age characteristics of children in the target age group(s);

6/23

- the age associated activities of children in the target age group(s) (e.g. school, nursery);
- the environment where the product is to be used (e.g. hospital or community);
- the condition to be treated;
- the condition related characteristics of the child (e.g. likely disabled, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to centrally nervous system diseases (e.g. epilepsy) or to critical illnesses);
- the 'criticality' of the dose (i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window) and how the dose is to be calculated;
- the maximum duration of therapy which can be foreseen;
- the availability of relevant safety data for the active substance, excipients and the finished medicinal product;
- the pharmaceutical properties of the drug substance (e.g. solubility, taste);
- patient acceptability i.e. child friendliness.

On this basis, the most sensitive development aspects are likely to arise in paediatric medicines for long term use in neonates, infants and young children, particularly when the excipients used are known to have their own undesirable properties, or when the safety [illegible] relevant to the target age

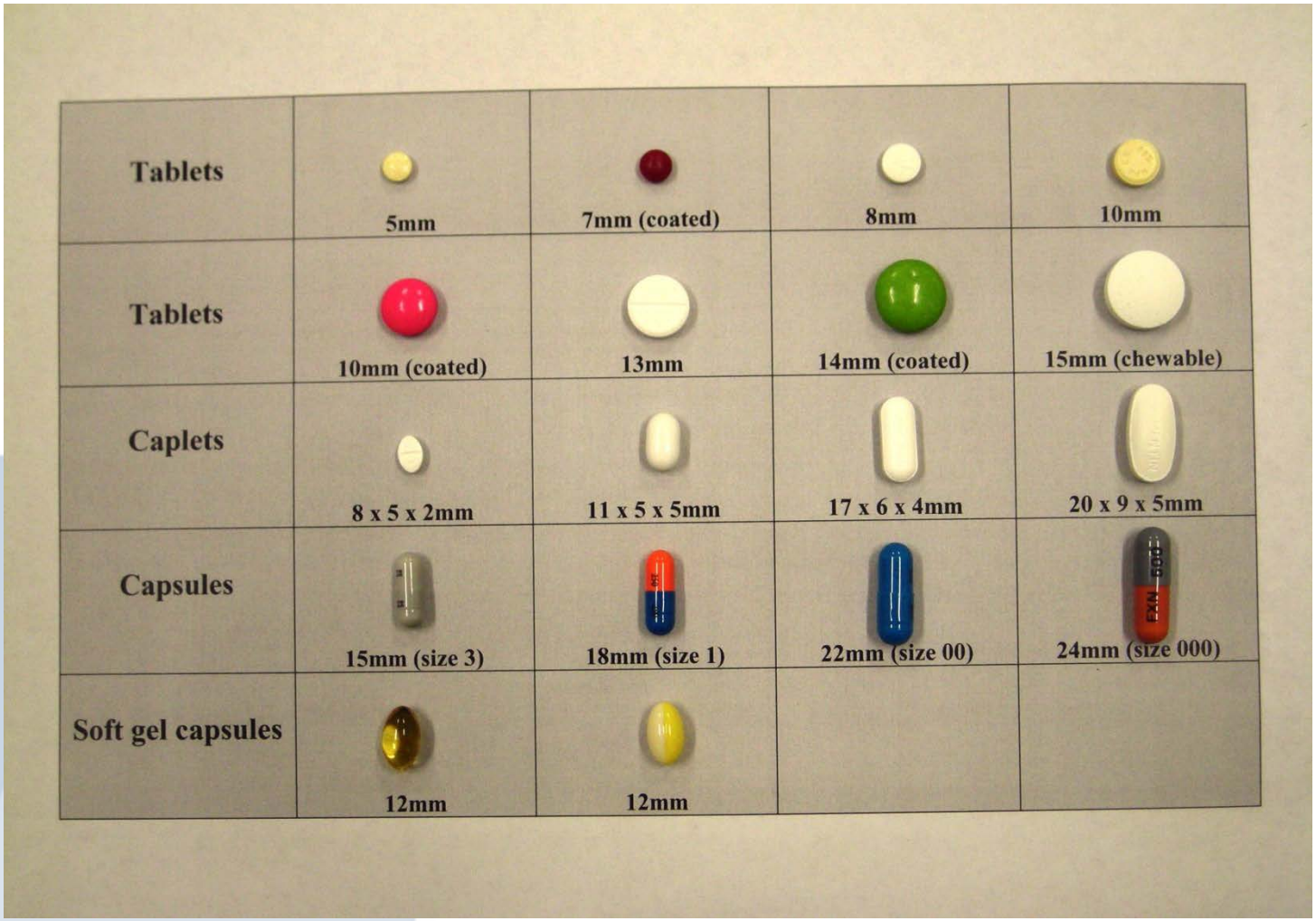
Major issues

- At what age can children take tablets or capsules?

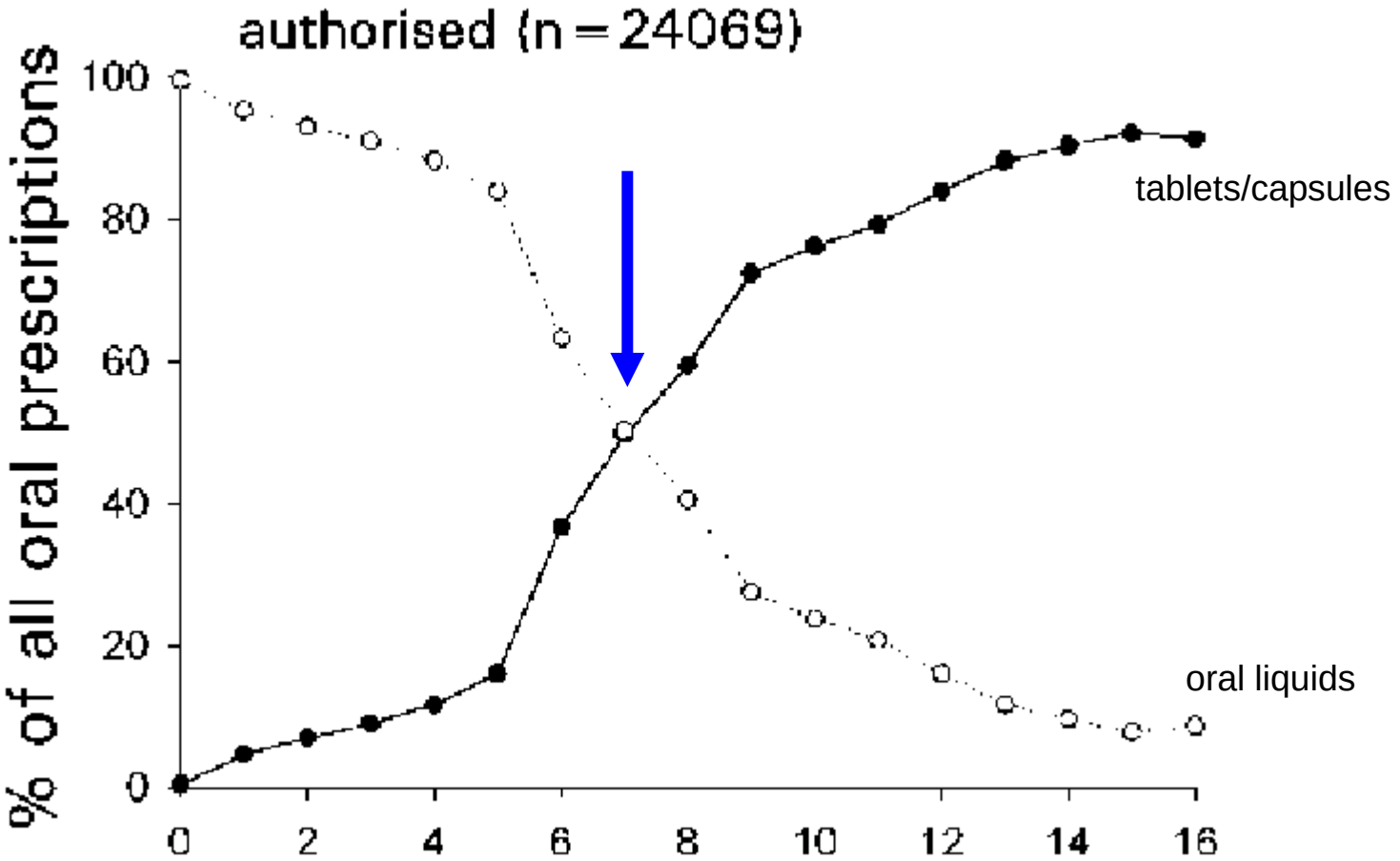
At what age can children take tablets or capsules?

- Important for
  - Safety
  - Commercially
    - Stability
    - Ease of formulation, manufacture, transport, storage, dispensing
    - cost
- Personal experience/anecdote
- Little literature
- Depends on
  - Size
  - Shape
  - Patient factors

Tablet and capsule sizes

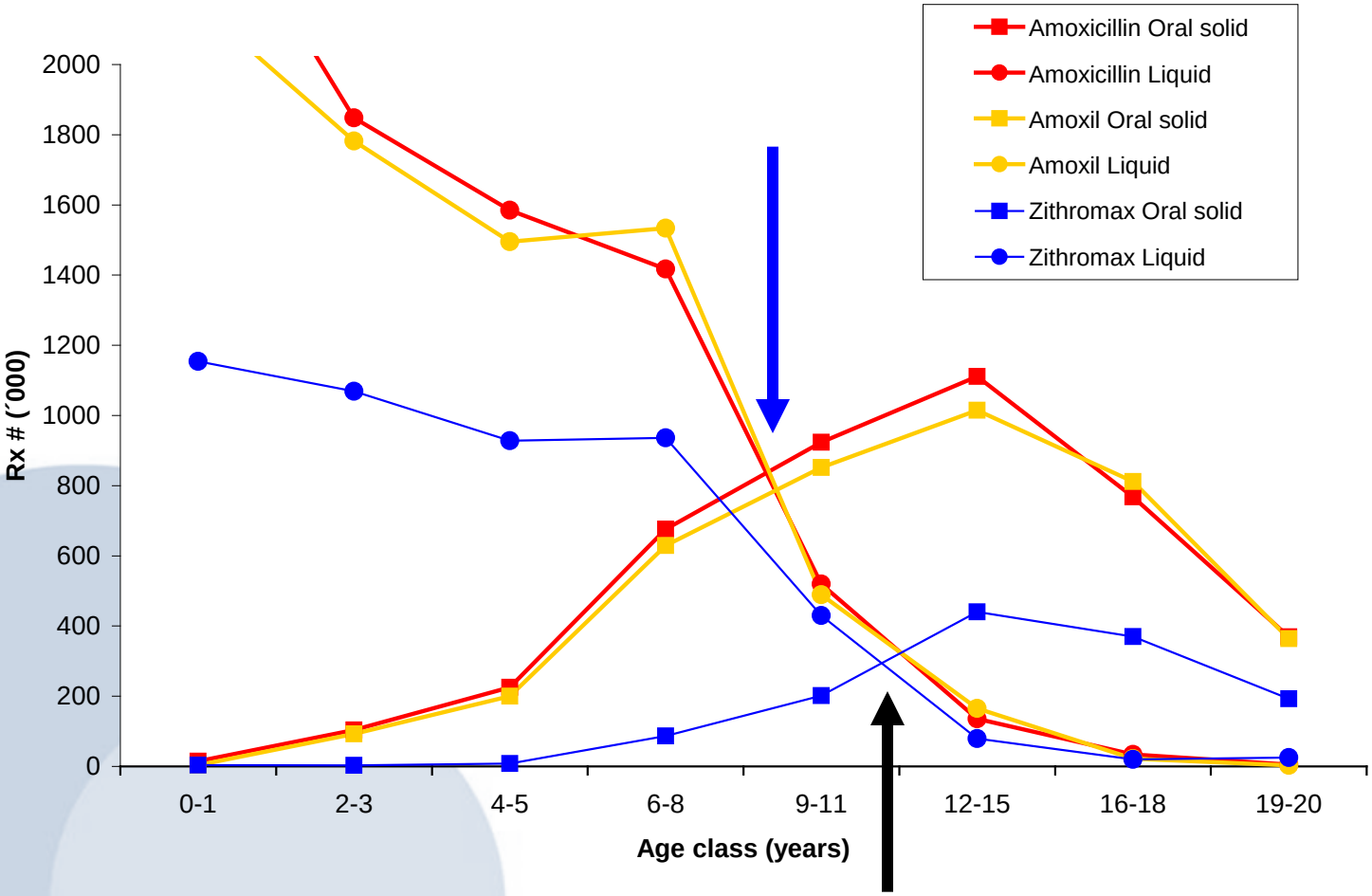


Prescriptions for authorised medicines – acceptance of dosage forms in Holland (2000)



From Schirm E et al. *Lack of appropriate formulations of medicines for children in the community*. Acta Paed 2003; 92: 1486-9

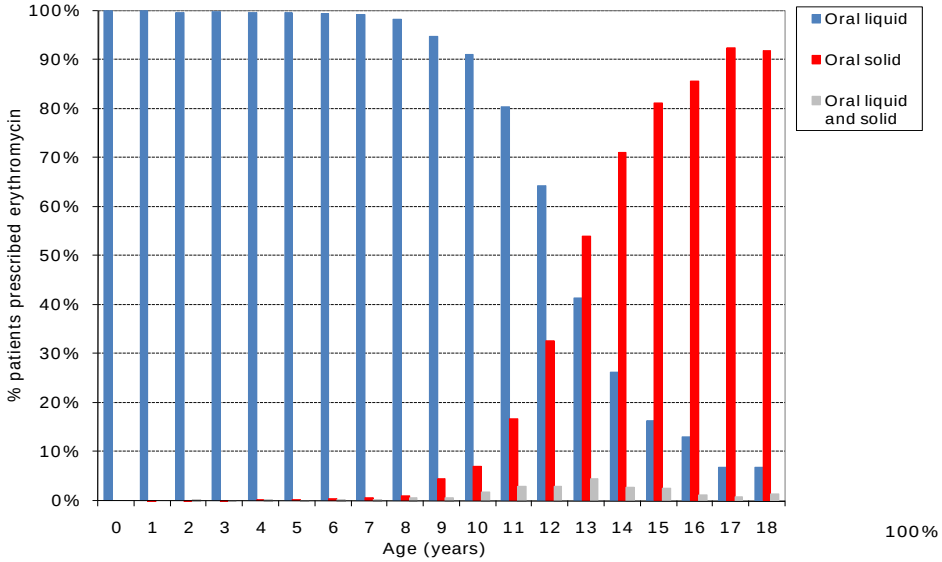
Antibiotics – acceptance of dosage forms in USA



Acknowledgement:-

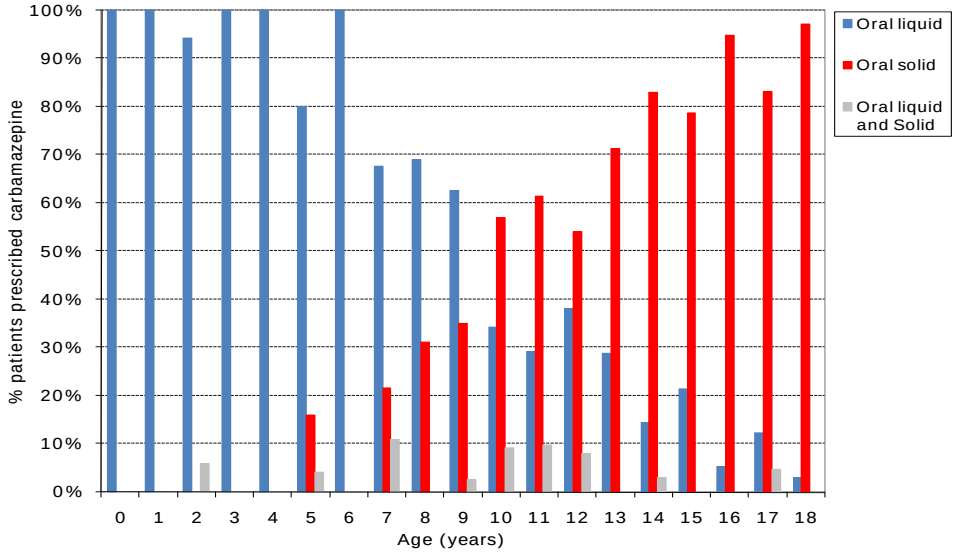
Despina Solomonidou, Novartis, Switzerland

At what age can children take tablets?



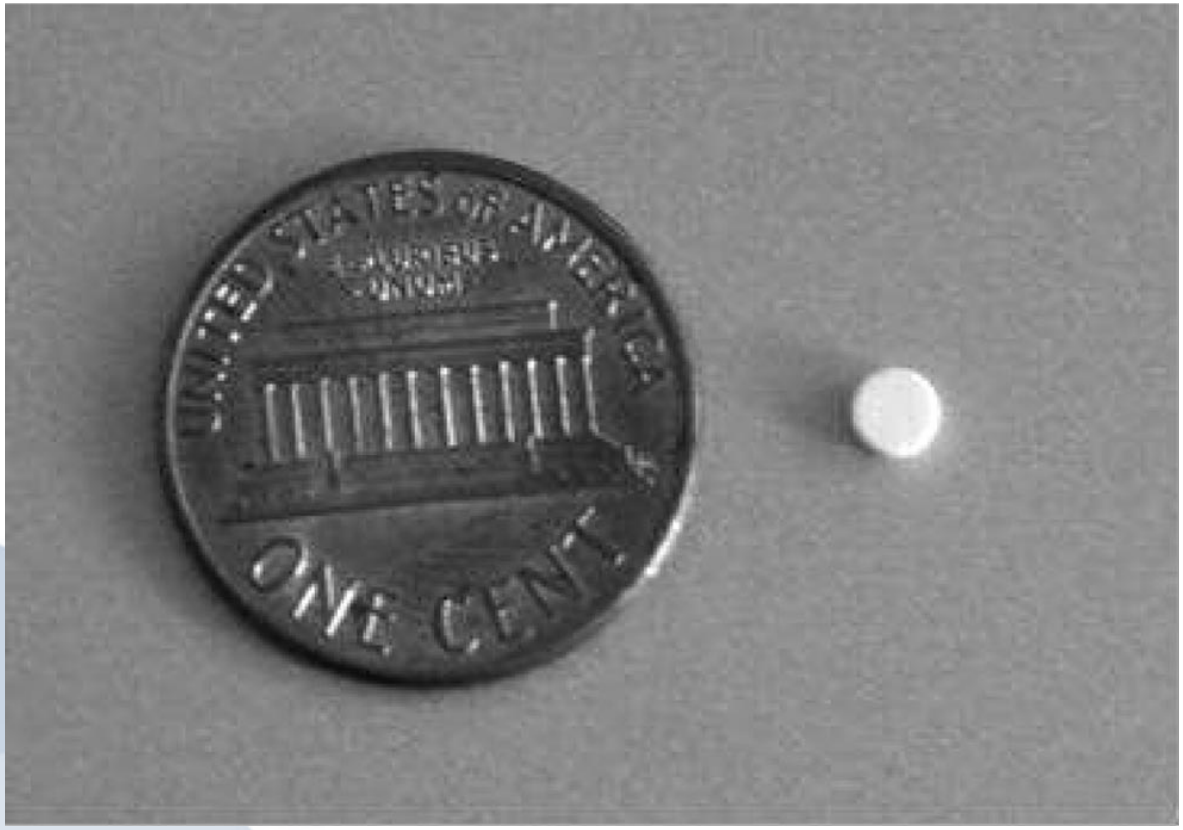
Erythromycin (acute)

Carbamazepine (chronic)



GPRD data. Tuleu C et al (in press)

Minitablets



Minitablet (3-mm diameter) next to a US penny.

Minitablets

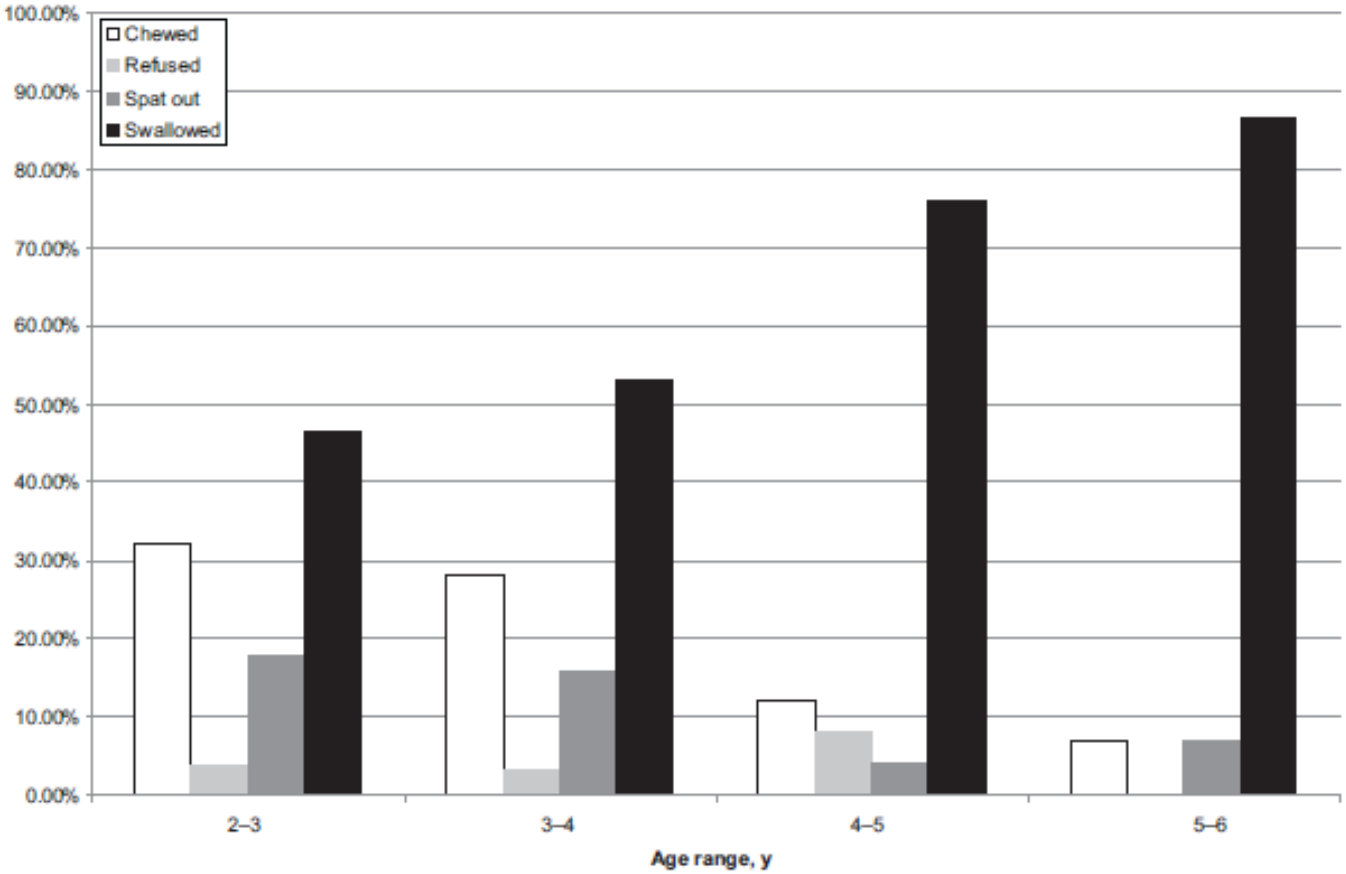
Minitablets: New Modality to Deliver Medicines to Preschool-Aged Children

Sarah A. Thomson, BSc[a,b], Catherine Tuleu, PhD[a,b,c], Ian C. K. Wong, PhD, MRPharmS[b,c], Simon Keady, MPharm[c,d], Kendal G. Pitt, PhD[e], Alastair G. Sutcliffe, MD, PhD, FRCPCH[f]

[a]Centre for Paediatric Pharmacy Research and [c]Department of Pharmaceutics, School of Pharmacy, University of London, London, England; [d]Pharmacy Department, University College London Hospitals, London, England; [e]Global Manufacturing Supplies, GlaxoSmithKline, Ware, England; [f]General and Adolescent Unit, University College Medical School, and [b]Institute of Child Health, University College London, London, England

Pediatrics 2009;123:e235–e238

Minitablets



Outcome expressed as percent per age range.

Major issues

- Strategy for those who cannot take tablets or capsules
  - Applicant to demonstrate that whole tablet or capsule is acceptable to the target age group
    - What % is considered appropriate?
  - Is crushing/opening (manipulation) an acceptable alternative strategy?
    - Affect of addition to food/liquid
    - Which foods/liquids?
    - Additional studies?
  - When should an alternative formulation be developed?

At what age can children take tablets?

238 **6.2.1. Powders, granules, pellets and tablets**

239 *Acceptability*

240 Powders, granules and pellets may be given to children from birth when administered as a solution. If
241 appropriately justified, the application of a liquid dispersion may be acceptable from birth as .

242 If powders, granules or pellets are administered in their solid form, they will normally be considered
243 acceptable from the moment the infant is able to accept solid . This is usually around six months
244 age. The risk of aspiration, choking and where relevant chewing should be considered depending on
245 the target age group, size, shape, quantity (volume) and the type of the active substance and dosage
246 form (e.g. gastro-resistant and modified release).

247 The tablet size is fundamental to the ability of a child to swallow a tablet. Young children may be able
248 to accept small tablets, but not large tablets. Unless otherwise justified by appropriate studies or
249 clinical evidence, small tablets (i.e. tablets from 3 to 5 mm diameter, width or length whichever is the
250 longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets
251 (i.e. tablets from 5 to 10 mm) for children below the age 6 years; large tablets (i.e. tablets from 10 to
252 15 mm) for children below the age of 12 years and very large tablets (i.e. tablets from 15 mm) for
253 children below the age of 18 ye .

254 For chronic diseases, tablet size acceptability in children may be improved by adequate training
255 techniques. Such training may allow a larger size for age groups than normally considered eptable.
256 Tablet size acceptability may also be improved by adequate instructions for joint intake with semi solid
257 food. In order to avoid a wide range of strengths, a single dose may normally involve several small
258 sized ta s.

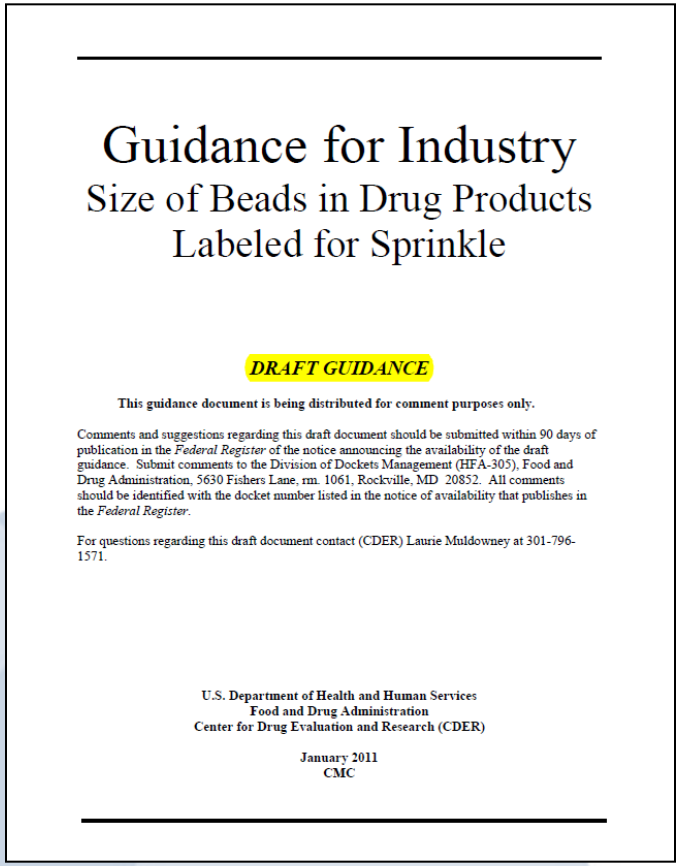
259 The suitability of tablets in children should be further justified in relation to the disease and the risks
260 associated to under-dosing, choking and asp on. Any identified risks should be carefully balanced
261 against the risks associated with the application of an alternative dosage form.

8/23

Age Group	Acceptable
3-5 yr	3-5 mm
6-11 yr	5-10 mm
12-17 yr	10-15 mm
18 yr and above	> 15 mm

Draft Guideline on Development of Medicines for Paediatric Use

Sprinkles – addition of capsule contents to food



Guidance for Industry

Size of Beads in Drug Products Labeled for Sprinkle

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Laurie Muldowney at 301-796-1571.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2011
CMC

- Capsule contents onto soft food
  - Often for SR
  - Swallow without chewing
- Maximum bead size 2 mm
- Enteral feeding tubes
  - Demonstrate passage of complete dose without blockage
- Bioequivalence
  - Demonstrate for SR products
  - No need to demonstrate for sprinkled immediate release

Major issues – oral liquids

- Acceptability
- Excipient nature and quantity
- Dose volume (maximum)

Age	Volume (max)
0-3 yr	5 ml
4-12 yr	10 ml

  - Drops
- Administration/dosing device
  - Accuracy
  - Dedicated v generic

Major issues

- Conventional v dispersible v oro-dispersible
  - Actual method of administration?
- Manipulation of dosage form
  - For ‘accurate’ administration of a smaller dose
    - See table on next slide
  - To achieve acceptable administration
    - Crush tablet; open capsule; measure liquid
    - Add to
      - Food
      - Liquid
      - Confectionery (candy)
- Extemporaneous compounding by the pharmacist
  - Is it ever appropriate?

Drug dosage form	Manipulation for dose accuracy includes
tablet	a. split/broken/cut and a segment given, or b. crushed and a portion of the powder given, or c. dispersed in liquid and a portion of the liquid given.
capsule	a. opened, dispersed in liquid and a portion of the liquid given, or b. opened and a portion of the powder given.
sachet (powder)	a. opened, dispersed in liquid and a portion of the liquid given, or b. opened and a portion of the powder given.
oral liquid	diluted and a portion given (to make the measurement of a small dose volume easier).
suppository	cut/split and a segment given.
nebuliser solution	a. portion given, or b. diluted and a portion given.
enema/bladder irrigation	a. portion of sachet/unit given (the remainder then discarded), or b. portion of contents removed and the remainder given.
transdermal patch	a. patch cut and a portion applied, or b. portion of patch uncovered and applied.
intravenous injection	a. reconstituted or ready prepared solution, further diluted to allow a smaller dose to be measured, or b. volume of fluid removed from IV container, drug added (to obtain accurate concentration for infusion).

Major issues - injections

- Dose volume and concentration
  - Smallest measurable volume?
    - Accuracy of syringes
    - Understanding of decimals in hundredths
  - Lowest flow rate for continuous infusion?
  - Dilution to achieve measurable volumes/flow rates
- Container size
  - In relation to dose to be measured
  - Avoiding 10 times errors
    - Paracetamol injection example
      - Dose at 3 months = 40 mg in 4 ml; smallest container = 50 ml
- Compatibility with common infusions and nutrition

Conclusion

- Children require dosage forms adapted to their ability and need for variable dose with age/weight
- Not much is known about the age appropriateness of different dosage forms
- Carers may take the view that any manipulation to achieve administration is OK.
- Applicants should be asked to demonstrate that the target age group can manage the dosage form or an alternate strategy should be proposed
- Questions remain about how far the applicant must go and what % of patients must find the strategy 'acceptable'.

Comments should be provided using this template. The completed comments form should be sent to qwp@ema.europa.eu

Keywords *child, pharmaceutical development, quality*

Note:

CHMP would like to bring to your attention the three points below for which further input (specific attention) is particularly awaited:

- 6. Route of administration and dosage form
  - 6.2.1: Powders, granules, pellets and tablets:
    - *Acceptability*: tablet size and young children,
    - *Sub-division of tablets*: Use of score lines to administer lower doses
- 9. Excipients in the formulation:
  - 9.1 General considerations: Safety of excipients.

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