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# Unique Features of Preclinical and Formulation Development of Paediatric Medicines

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# Preclinical development of paediatric medicines in a nutshell

# Preclinical Investigation for paediatric medicines

- In the past, many medicines authorised in Europe were not studied adequately or authorised in children

- Children represent a vulnerable population group with developmental, physiological and psychological differences from adults

- They are not merely ‘small adults’. Age- and development-related research, and the availability of suitable medicinal products, is consequently particularly important

# Preclinical Investigation for paediatric medicines

**Pre-term Infant**

< 36 weeks of gestation

**Term Newborn Infant**

0-27 days

**Infant/Toddler**

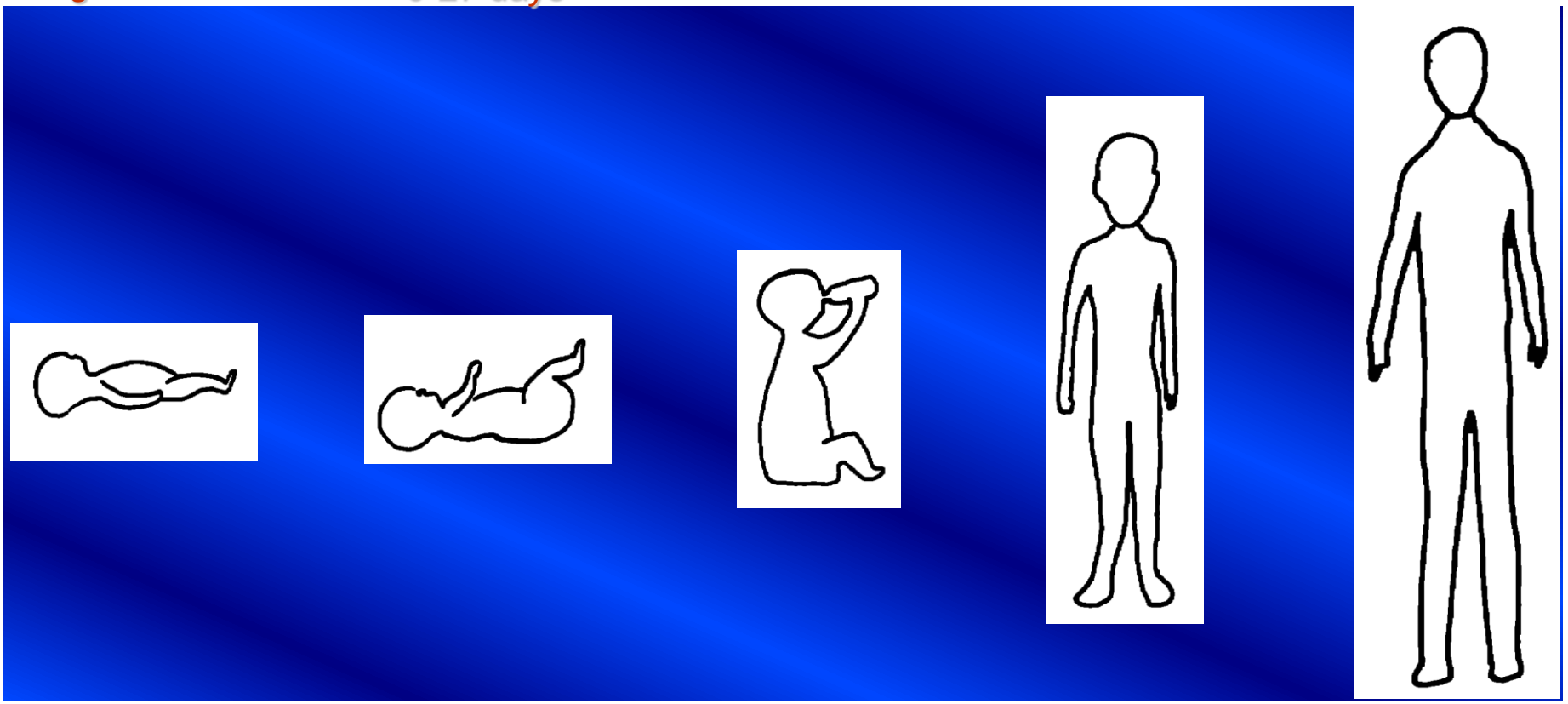
28 days -23 months

**Child**

2 - 11 years

**Adolescent**

12 –18 years



**Survival** **Adaptation** **Growth** **Training** **Maturation**

# Preclinical Investigation for paediatric medicines

- Agency took the responsibilities in 2007 to stimulate research into the uses of medicines in children and to lead to their authorisation in all ages
- REGULATION (EC) No 1901/2006 on medicinal products for paediatric use
- The Regulation came into force on 26 January 2007.

  The objective of the Paediatric Regulation is to facilitate the development and availability of medicines for children from birth to less than 18 years,
  - ensuring that medicines for use in children are of high quality, ethically researched, and authorised appropriately,
  - improving the availability of information on the use of medicines for children

# Preclinical Investigation for paediatric medicines

- All applications for marketing authorisation for new medicines that were not authorised in the EU before 26 January 2007 have to include the results of studies carried out in children of different ages

- The **PDCO** (**Paediatric Committee**) determines what these studies must be and describes these in **paediatric investigation plans** (**PIPs**)

- This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorised and patented

# Preclinical Investigation for paediatric medicines

## Organ systems at highest risk for drug toxicity are those that undergo significant postnatal development

- Brain, where neural development continues through adolescence (Rice and Barone 2000)
- Kidneys, where adult levels of function are first reached at approximately 1 year of age (Radde 1985)
- Lungs, where most alveolar maturation occurs in the first 2 years of life (Burri 1997)
- Immune system, where adult levels of IgG and IgA antibody responses are not achieved until about 5 and 12 years of age, respectively (Miyawaki et al. 1981)
- Reproductive system, where maturation is not completed until adolescence (Zoetis and Walls 2003)
- Skeletal system, where maturation continues well into adulthood for 25-30 years (Zoetis and Walls 2003)
- Gastrointestinal systems, which may have direct consequences on bioavailability, clearance, and biotransformation of drugs are functionally mature by about 1 year of age (Walthall 2005)

# Preclinical Investigation for paediatric medicines

## Pharmacokinetics in paediatrics

| | | |
|---|---|---|
| **Absorption** | Reduced gastric motility<br>Lack of intestinal flora | •Gastric emptying time 87min vs. 65 in adults; less peristalsis<br>•Decreased first pass effect<br>•Approaches adult values at 6-12 months |
| **Distribution** | Increased body water content<br>Less body fat<br>Less serum albumin | •80% in a newborn vs. 60% in an adult<br>•Larger volume of distribution for water-soluble drugs<br>•Larger doses by weight (mg/kg) |
| **Metabolism** | Not all CYP450 Enzymes are present at birth<br>Formation not linear | •CYP2D6 **increases rapidly after birth**<br>•CYP3A4, CYP2C9, and CYP2C19 appear within the **first month** of life<br>•CYP1A2 activity comes at **1 to 3** months<br>•CYP1A2, CYP2C9, and CYP3A4 **exceed** adult capacity by **6 to 12 months** of life, decline to adult values after puberty |
| **Excretion** | Decreased GFR in neonate<br>Decreased tubular reabsorption in infants.<br>Transporter (secretory) systems in the proximal tubule are deficient at birth | •Slower clearance = longer t1/2<br>•Faster renal excretion in infants<br>•Less frequent dosing interval needed to avoid accumulation and toxicity |

# Preclinical Investigation for paediatric medicines

- **Acetaminophen** — Acute acetaminophen toxicity is a classic example of how maturation can affect the toxicity profile of a drug. Young children are far less susceptible to acute acetaminophen toxicity than adults because children possess a higher rate of glutathione turnover and more active sulfation. Thus, they have a greater capacity to metabolize and detoxify an overdose of acetaminophen when compared to adults (Insel 1996)


- **Valproic acid** — In contrast to acetaminophen, young children treated with valproic acid appear disproportionately vulnerable to **fatal hepatotoxicity** (Dreifuss et al. 1987)

- **Chloramphenicol** — Chloramphenicol is associated with **mortality in newborns** because exposure is increased due to a longer half-life (t½ = 26 h) compared to adults (t½ = 4 h) (Kapusink-Uner et al. 1996)

  *Il cloramfenicolo ha efficacia contro un'estesa varietà di microrganismi,ma per via dei seri effetti collaterali (come i danni al midollo osseo, inclusa l'anemia aplastica o la sindrome del bambino grigio nella somministrazione pediatrica), il suo impiego negli esseri umani viene preferibilmente limitato al trattamento d'infezioni gravi, con rischio di morte del paziente e per le quali non esista un'alternativa di pari efficacia (ad esempio per la febbre tifoide).*


- **Inhaled corticosteroids** — Inhaled corticosteroids have been found to decrease growth velocity in children, an irrelevant endpoint in adults

- **Aspirin** — Aspirin should not be used to treat children with influenza or varicella infections because of their increased risk of developing Reye's syndrome, a complication not seen in adults (Belay et al. 1999)

  *La **Sindrome di Reye** è una malattia acuta, dall'esito potenzialmente letale, che colpisce quasi esclusivamente i bambini. È caratterizzata da manifestazioni patologiche che riguardano prevalentemente il cervello e il fegato, con encefalopatia acuta e steatosi epatica, che insorgono rapidamente nel corso di un'infezione virale, spesso dopo l'assunzione di farmaci a base di acido acetilsalicilico*

# Preclinical Investigation for paediatric medicines

- Sufficient safety information to support initiating studies in the pediatric population
  - Clinical studies in adults
    - Other pediatric populations
  - Nonclinical studies in adult animals
    - General toxicity studies
    - Core safety pharmacology package
    - Standard battery of genotoxicity tests
    - Reproductive and developmental toxicity studies
    - **Juvenile animals toxicity studies**

# Why juvenile toxicity studies (I)

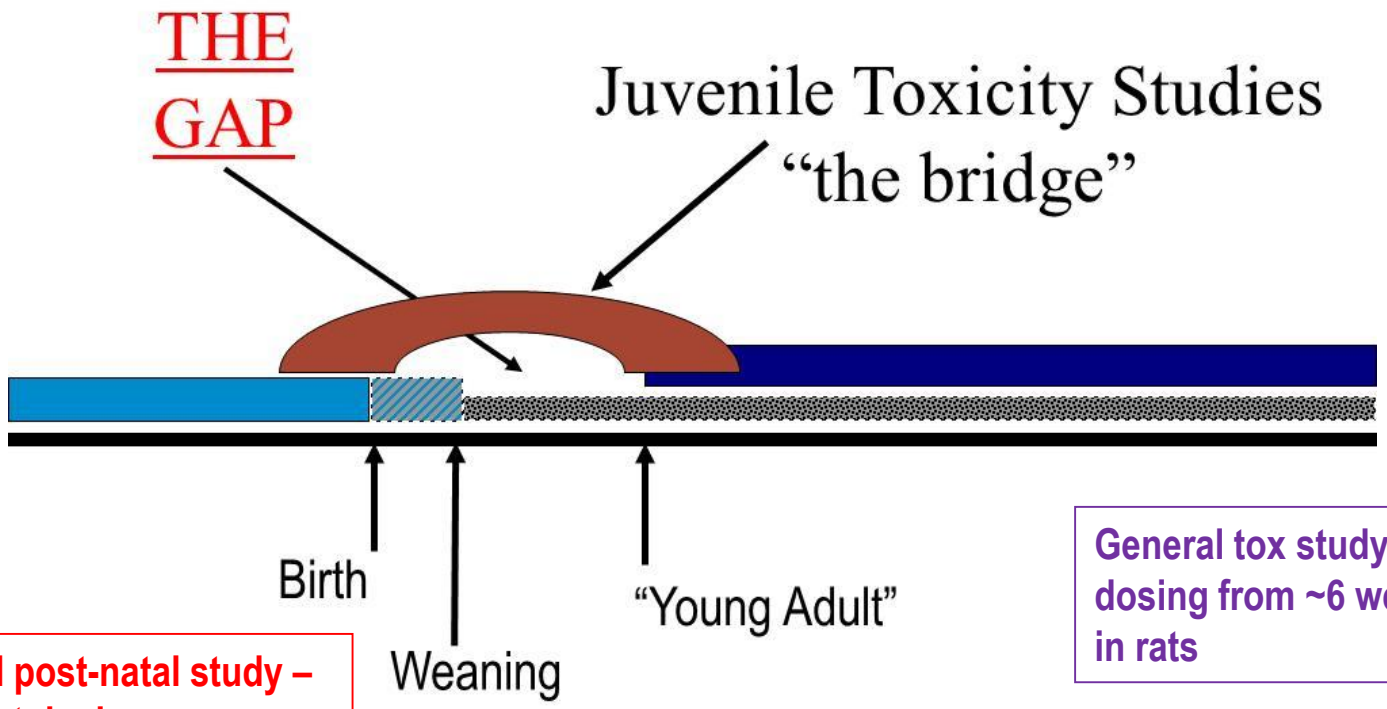
- Situations that would justify toxicity studies in juvenile animals include, but are not limited to:
  - When the indication is specifically targeted for children
  - Findings in non-clinical studies that indicate target organ or systemic toxicity relevant for developing systems
  - Possible effects on growth and development in the intended age group
  - If a pharmacological effect of the test compound could/would affect developing organs
  - Unique chemical class or unique combination product

# Why juvenile toxicity studies (II)

- Young animals in general exhibit developmental characteristics similar to pediatric patients
- They are considered appropriate models for assessing drug effects in this population
- Data from juvenile animal studies can contribute to the assessment of potential drug toxicity in the pediatric population
- Provide information that might not be derived from standard toxicology studies using adult animals, or safety information from adult humans

# Why juvenile toxicity studies (III)

To obtain information on potentially different safety profiles from those seen in adults – bridging the gap between reprotox and repeat dose tox studies

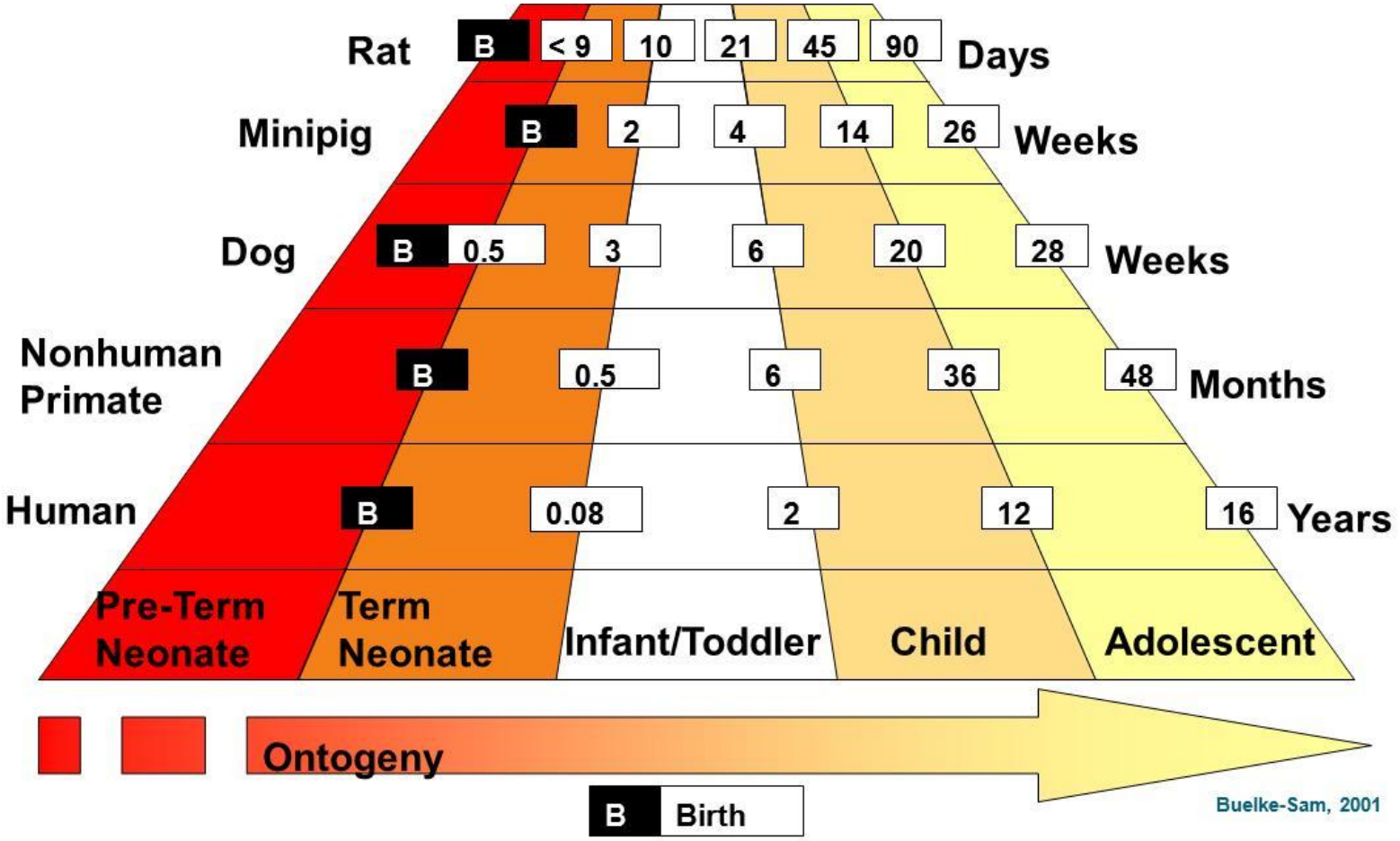



Pre and post-natal study – no direct dosing

General tox study – direct dosing from ~6 weeks of age in rats

# Preclinical Investigation for paediatric medicines

## Comparative age categories



# Preclinical Investigation for paediatric medicines

## Structural and Functional Development

### Human

Nervous system: up to adulthood.

Pulmonary system: up to 2 yrs

Reproductive system: up to adulthood

Renal system (anatomical): GW35

Renal system (functional): up to 1 year

Immune system: up to adulthood

Liver: depending on the endpoint: differences in functioning of drug-metabolising enzymes, transporters, etc. during the first months → ca 3years

### Rat

Brain: by ~ 35 days.

Pulmonary system: by 28-35 days.

Reproductive system: ~35/45 days (F/M).

Renal system (anatomical): 4-6 weeks.

Renal system (functional): ~ 21 days.

Immune system: by ~ 60 days.

Liver: adult structure reached by ~28 days. Enzyme/transporter activity still not clearly understood, but P450 considered to be ~ 45 days.

# Preclinical Investigation for paediatric medicines

## Study design considerations

- Dose selection
  - Exaggerated toxicity not desirable, aim is to detect any possible increase in sensitivity of young vs adults
- Preliminary study essential
  - To assess tolerability/dose-range
- Inclusion of TK essential
- Endpoints
  - Numerous and flexible
    - Each study has tailor-made design
- Numbers per sex per group not standard
  - Depends on endpoints
- Practical issues

# Preclinical Investigation for paediatric medicines

## ITFXXX - Juvenile tox study in rats

- Study Design
  - Dose: 0, 20, 60, 180 mg/kg,  oral treatment by gavage
  - Treatment duration: 28 days starting from post-weaning pups (PND 21)
  - Animals observed till maturity achievement
  - Numbers per sex per group: 20M+20F
  - Satellite animals for toxicokinetics: 15M+15F

- Endpoints
  - Body weight and food consumption, clinical signs, haematology and clinical chemistry, urine analysis
  - Growth measurements (tibia length)
  - Behavioural tests (open field and auditory startle reflex)
  - Sexual maturation, mating performance and fertility
  - Gestation

# ITFXXX - Juvenile tox study in rats

- Results
  - Hematology and clinical chemistry: Modifications comparable to adult animals
  - Tibia lenghts were similar between control and treated groups 6 weeks after the end of treatment
  - Sexual maturity achievement was comparable in all groups
  - Open field test: no effect at any dose, exploratory behavior comparable in all groups (M and F)
  - Auditory startle response: no evidence of adverse influence of treatment
  - Reproduction
    - No effect on mating performance and fertility in any group
    - No effects on mean numbers of corpora lutea and implantations and viable embryos
  - Toxicokinetics showed comparable plasma levels between young and adult rats

# ITFXXX - Juvenile study in rats

- Conclusions
  - Safety profile similar to adult animals, previous toxicological data in adults transferable to youth
  - No effects on growth and development
  - Reproduction performance not affected by treatment with the drug

Treatment of paediatric population admitted starting from 2 years
Dose defined on a mg/kg base

# Formulation development of paediatric medicines in a nutshell

# Appropriate dosage form for children CRITERIA

**A medicine designed for use in Paediatric Patients must consider the following:**

- Patient population variability (age development)
- The need for dose flexibility
- Excipient tolerability
- Easy and safe administration
- Patients and parents compliance (dosage form child can take/caregiver can administer)

# AGE DEVELOPMENT AND DOSAGE FORMS OF CHOICE

| 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)* |
|---|---|---|---|---|---|---|
| **Peroral** | | | | | | |
| Solution/ Drops | 2 | 4 | 5 | 5 | 4 | 4 |
| Emulsion/ Suspension | 2 | 3 | 4 | 5 | 4 | 4 |
| Effervescent DF* | 2 | 4 | 5 | 5 | 4 | 4 |
| Powders/ Multiparticulates | 1 | 2 | 2 | 4 | 4 | 5 |
| Tablets | 1 | 1 | 1 | 3 | 4 | 5 |
| Capsules | 1 | 1 | 1 | 2 | 4 | 5 |
| Orodispersable DF | 1 | 2 | 3 | 4 | 5 | 5 |
| Chewable tablets | 1 | 1 | 1 | 3 | 5 | 5 |

REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION; 28 July 2006; EMEA/CHMP/PEG/194810/2005

For the early ages the code indicates mainly the applicability of the route and the dosage form:

**1 not applicable**
**2 applicable with problems**
**3 probably applicable, but not preferred,**
**4 good applicability**
**5 best and preferred applicability**

For the higher ages more or less all dosage forms might be principally applicable, but with increasing age the preference of the children becomes more important

**1 not accepted**
**2 accepted under reserve**
**3 acceptable**
**4 preferred acceptability**
**5 dosage form of choice**

# FLEXIBILITY IN DOSAGE AND ACCEPTABILITY (1)

- Children are often unable to swallow pills or capsules until they are 6 (or 7 or 12 **or never**) years of age
- Traditionally pediatric dosing is weight based (mg/kg)

## The Paediatric Holy Grail

**An**
**Oral**
**Liquid**
**Preparation**

For every new chemical entity and currently marketed drug still under patent, *with or without* safety and effectiveness data in children, where *no oral liquid dosage form is available*, the manufacturer should be required to provide a formulation that effectively converts an oral solid or intravenous dosage form to an oral solution or suspension dosage form.

**Statement of the Paediatric Pharmacy Advocacy Group http://www.ppag.org/**

# FLEXIBILITY IN DOSAGE AND ACCEPTABILITY (2)

## Experience with ITFXXX

**New Chemical Entity initially developed as capsule dosage form in adults found potentially suitable for a specific indication in children**

- Clinical needs: mg/Kg dosage for Phase 1-2 studies, wide dose and weight ranges (0.5-5mg/kg, 10-50 or more Kg children)
  - **No oral solid formulation** possible to match the clinical needs
- API: low solubility in water/buffered solutions (< 1mg/mL) and very bad taste in solution
- API: costly and available in limited amount
  - **No oral solution** formulation possible to match the clinical needs
  - No sufficient API and time available to explore API coating

⇓

**DEVELOPMENT OF AN ORAL SUSPENSION FORMULATION**

- minimized API solubilization thus minimizing taste and stability
- great dose flexibility and wide age applicability / acceptability

# FLEXIBILITY IN DOSAGE AND ACCEPTABILITY (3)

## Experience with ITFXXX

SIX different capsules

cm.

3
2
1

| DOSE | 100 mg | 75 mg | 50 mg | 37.5 mg | **25 - 12.5 – 10 – 7.5mg** |
|---|---|---|---|---|---|
| Cps size |   |   |   |   |   |

**ONE oral suspension formulation**

| DOSE | 100 mg | 75 mg | 50 mg | 37.5 mg | 25 mg | 12.5 mg |
|---|---|---|---|---|---|---|
| mL (1% w/v) | 10 | 7.5 | 5 | 3.75 | 2.5 | 1.25 |

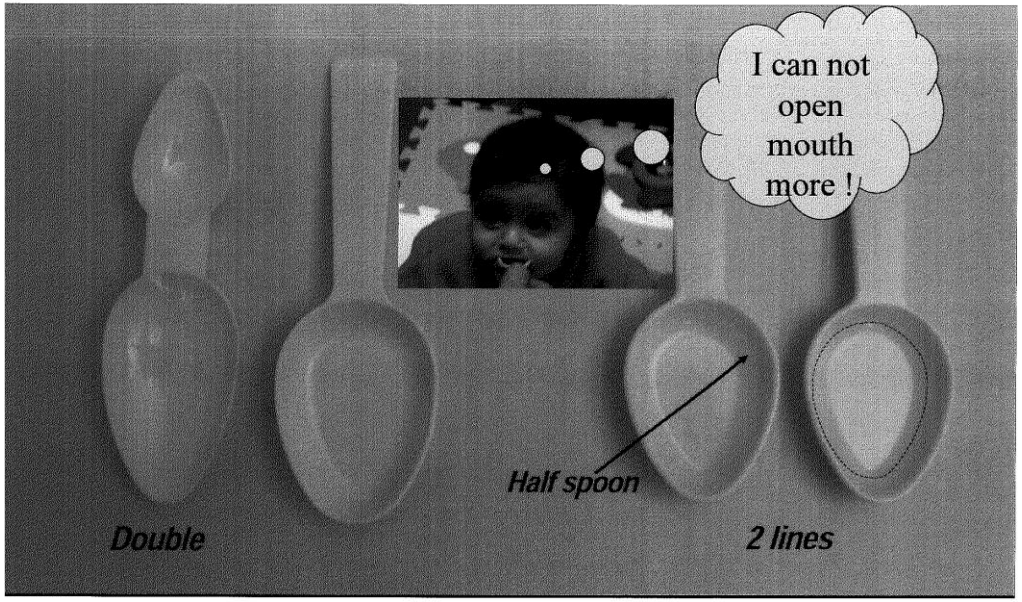
ONE bottle equipped with one or more syringes suitable for oral administration as delivery device

**and ONE Placebo formulation only as well !!!**

# Oral Liquid Formulations for Children
## – The Device –

- Measuring spoons and cups are generally not recommended for the administration of drugs with a narrow therapeutic index.

- Graduated pipettes and oral syringes are particularly convenient for infants and young children who are not able to use either spoons or cups and allow accurate dose measurement and controlled administration to the buccal cavity for all ages. Oral syringes must not be capable of accepting a needle or connecting to intravenous devices; thus preventing accidental parenteral injection of the liquid.

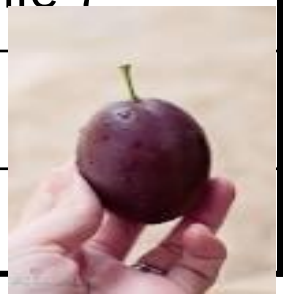



**Example 1: Exacta MED oral syringes (Baxter)**
- 0.5, 1, 3, 5, 10, 20, 35 and 60 mL
- clearly marked graduations help promote accurate volume identification
- dispenser tip designed to prevent wrong-route administration

**Example 2: Safe & Easy (Bormioli Rocco)**
- packaging solution that ensures total safety and practicality in administering syrups to infants and children.
- no longer risks of plug detachment

# Oral Liquid Formulations for Children
## – The Down Side –

- Suspensions may result in unequal drug delivery over time due to non-uniform re-dispersibility
- Liquid formulations may have palatability problems due to both taste and texture
- Volume of administration to be carefully evaluated in pre-term and new born infants

| | Day of life 1 | Day of life 3 | Day of life 7 |
|---|---|---|---|
| Stomach size | Glass marble  | Ping-pong ball  | Plum  |
| Stomach volume | 5-8 mL | - | 30-50 mL |

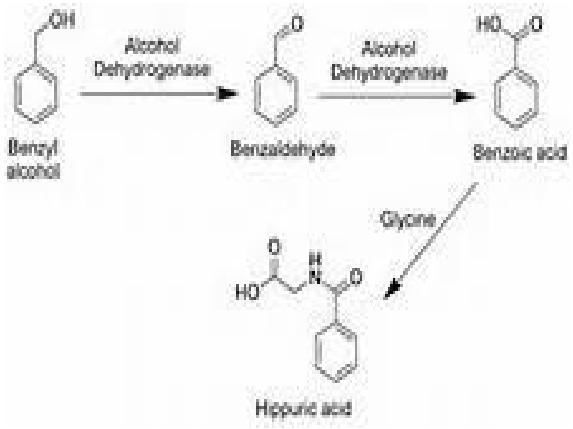
**The small functional volume of the stomach combined with the frequent feedings and the young infant's propensity to reflux, highlights the need for formulator to carefully consider drug concentration so that drug dose can be successfully titrated for weight and still be delivered in a volume that is tolerated by the infants**

Liquid formulations may contain potentially toxic excipients (co-solubilizers, surface active agents, preservatives)

# THE COMPOUNDS WE ROUTINELY ADMINISTER BUT NEVER PRESCRIBE : EXCIPIENTS (1)

In 1981, Gershaniket al. reported cases of “gasping syndrome”due to use of bacteriostatic normal saline containing 0.9% **Benzyl Alcohol**

- Pre-term infants exhibited: severe metabolic acidosis, hepatic/renal failure, signs of neurological deterioration and gasping respiration
- Unmetabolizedbenzyl alcohol (benzoic acid) was in the urine
- Conjugation of benzoic acid to hippuricacid is deficient in premature infants




E-Ferol = Vitamin E plus **Polysorbate80**

- Classified as “one of the most deadly pharmaceutical errors in American history”
- Premature babies exposed to E-Ferol began to exhibit hepatomegaly, thrombocytopenia, cholestaticjaundice, ascitesand azotemia.
- There were 40 infant deaths associated with E-Ferol;
- Cause of illness was not established, suspected elevated levels of polysorbate
- O'Neal/Jones & Feldman Pharmaceuticals began marketing E-Ferol in the fall of 1983 as a vitamin supplement. *The product was never submitted for FDA approval.*


http://www.lawyersandsettlements.com/articles/wrongful_death/interview-wrongful-death-law-14533.html

# THE COMPOUNDS WE ROUTINELY ADMINISTER BUT NEVER PRESCRIBE: EXCIPIENTS (2)

## Preservatives: Benzyl Alcohol / Benzoic Acid / Benzoates

- Benzyl alcohol is often used as a preservative in injectable medicinal products.
- It must not be given to neonates due to their immature metabolism.
- In developing pharmaceutical preparations for use in young paediatric patients up to three years old, benzyl alcohol should be carefully evaluated and may best be avoided.
- Benzoic acid, sodium benzoate and potassium benzoate when used in parenteral dosage forms may increase the risk of jaundice in neonates.

## Co-solvents: Propylene Glycol

- Propylene glycol is used as a solvent in oral, topical and injectable medications, often for substances, which are not highly soluble in water, e.g. phenobarbital, phenytoin and diazepam. It is also commonly used in injectable multivitamin concentrates.
- Paediatric patients below 4 years have a limited metabolic pathway (alcohol dehydrogenase), therefore accumulation of propylene glycol can occur in the body.
- Main toxic action is depression of the central nervous system. High osmotic pressure may cause laxative effects. Topical administration has been reported to cause contact dermatitis

# THE COMPOUNDS WE ROUTINELY ADMINISTER BUT NEVER PRESCRIBE: EXCIPIENTS (3)

## Sweeteners

**Table II: Selection of excipients for oral pediatric formulations, contributions to osmolar laxative effects and carbohydrate content at nominal usage (Section references 10–22, on page s65).**

| Excipient | Pharmacopoeial status | Energy (kJ/g) | Relative sweetness intensity* | Equi-osmolar quantities | IIG (maximum in oral solution, %) | Usage range (w/w%) | Clinical tolerance |
|---|---|---|---|---|---|---|---|
| Erythritol | PhEur, JP, GRAS | 0.4 | 0.7 | 6.7 | Not listed | ———— | ~ 10 g dose at ~0.3 g/kg body weight |
| Fructose | USP, BP, PhEur, JP, IIG | 16.3 | 1.17 | ~10 | 25% | < 25% | > 25 g/day |
| Glycerin | USP, BP, PhEur, JP, IIG | ~19.0 | 0.5–0.7 | ~5.3 | 95% listed | < 20% (preservative) | ~1.5 g/kg |
| Isomalt | BP, PhEur, GRAS | 11.7–13.4 | 0.4 | 20 | Not listed (for solution) | Not applicable | ~ 25 g/day (children) |
| Mannitol | USP, BP, PhEur, JP, GRAS | 6.7 (1.6 kcal/g) | 0.5 | 10 | 20–29.36%** | Typically < 10% | < 10 g/day (adults) |
| Raffinose | Naturally occurring trisaccharide† | ~15.8 | 0.2 | 32.6 | Not listed | ———— | ~ 30 g (adults) |
| Sorbitol | USP, BP, PhEur, JP, IIG | 7.5–13.8 (1.8–3.3 kcal/g) | 0.6 | 10 | Maximum < 35% | preference ~ 20% | < 20 g/day (adults) < 0.5 g/kg (child) |
| Sucrose | USP, BP, PhEur, JP, IIG, GRAS | 16.5 | 1 | ~18 | 72% listed | < 66% (syrup) | > 25 g/day (children) |
| Xylitol | USP, BP, PhEur, JP, IIG, GRAS | ~10 | 0.95 | 8.3 | Listed as < 30% | Maximum < 10% for osmotic catharsis | ~ 10 g/day (children); adults, ~20 g/day < .37 g/kg/day |

* Sucrose is used as a standard. The relative sweetness intensity of source is 1.
** As oral powder for suspension/reconstitution.
† Is consumed as part of a normal diet.
BP is *British Pharmacopoeia*; GRAS is generally regarded as safe; IIG is the *Inactive Ingredients Guide*, US Food and Drug Administration; JP is *Japanese Pharmacopoeia*; PhEur is *European Pharmacopoeia*; USP is *United States Pharmacopeia*.

P. Van Arnum "Pediatric Formulations: Technical and Regulatory Considerations" , Pharmaceutical Technology, Aug 2009

# THE COMPOUNDS WE ROUTINELY ADMINISTER BUT NEVER PRESCRIBE: EXCIPIENTS (4)

**US commercially available oral pediatric formulations (Physician's Desk Reference 2007)**

| Taste and Sensory | | Solid Formulations | | Solution and Suspension Formulations | | |
|---|---|---|---|---|---|---|
| Flavors | Sweeteners | Bulk/diluter | Coatings | Solvents | Buffers/pH modifiers | Preservatives |
| Anise | Acesulfame potassium | Lactose | Cellulose acetate | Castor oil | Acetic acid | Benzoic acid |
| Banana | Aspartame | Maltodextrin | Dibutyl sebacate | Ethanol | Ascorbic acid | Butylated hydroxy anisole |
| Blackcurrant | High fructose corn syrup | Mannitol | Ethylcellulose | Glycerin | Calcium carbonate | Butylated hydroxy toluene |
| Bubble gum | Magnasweet | Microcrystalline cellulose | Stearic acid | Medium-chain triglyceride | Calcium phosphate | Butylparaben |
| Cherry | Maltol | Sorbitol | Triethyl citrate | PEG 400 | Citric acid | EDTA |
| Cotton candy | Saccharin | Starch | Copolymers | PEG 3350 | Hydrochloric acid | Methylparaben |
| Creamy caramel | Saccharin sodium | Sucrose | Ammonium methacrylate | Propylene glycol | Magnesium carbonate | Methylparaben sodium |
| Crème de vanilla | Sucralose | Xylitol | Butylated methacrylate | Vegetable oil | Magnesium hydroxide | Potassium sorbate |
| Fruit punch | Aroma | Binder | Carbomer 934P | Water | Malic acid | Propylparaben |
| Grape | Menthol | Crospovidone | Polyacrylate methacrylate | Surfactants | Potassium phosphate | Propylparaben sodium |
| Lemon crème | Yellow-plum-lemon aroma | Povidone | Lubricants | Docusate sodium | Sodium bicarbonate | Sodium benzoate |
| Mandarin orange | | Pregelatinized starch | Magnesium stearate | Glycerol stearate | Sodium citrate | Sorbic acid |
| Mint | | Disintegrants | Stearic acid | Lecithin | Sodium hydroxide | Isotonicifier |
| Mixed fruit | | Croscarmellose sodium | Glidant | Poloxamer 188 | Sodium phosphate | Sodium chloride |
| Orange | | Sodium starch glycolate | Silicon dioxide | Poloxamer 331 | Succinic acid | Mannitol |
| Peach | | | | Poloxamer 407 | Suspending/dispersing agents | Antifoam |
| Peppermint | | | | Polyoxyl 8 stearate (Macrogol stearate) | Acacia | Simethicone |
| Strawberry and banana | | | | Polyoxyl 35 castor oil (Cremophor EL) | Guar gum | Dimethicone |
| Strawberry and cream | | | | Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) | Carboxymethyl cellulose sodium | |
| Strawberry and mint | | | | TPGS | Crospovidone | |
| Tutti-frutti | | | | Polysorbate 20 | Hydroxypropyl cellulose | |
| Vanilla | | | | Polysorbate 80 | Hydroxypropyl methylcellulose | |
| | | | | Sodium lauryl sulfate | Povidone | |
| | | | | | Propylene glycol alginate | |
| | | | | | Sodium alginate | |
| | | | | | Tragacanth | |
| | | | | | Xanthan Gum | |

# THE COMPOUNDS WE ROUTINELY ADMINISTER BUT NEVER PRESCRIBE: EXCIPIENTS (5)

## LAST BUT NOT LEAST : most of PDCO observations at time of PIP presentation and discussion are related to excipients

**FDA Inactive Ingredients Database**
http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm

**STEP (Safety and Toxicity of Excipients for Paediatrics) Database**
http://www.eupfi.org

**ESNEE (European Study for Neonatal Excipient Exposure) Research Initiative**
Turner MA, Storme T. European Study for Neonatal Excipient Exposure (ESNEE) Eur J Hosp Pharm. 2012;19:67.

**Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product** CHMP/QWP/396951/06, revised 2008

**Excipients in the Label and Package leaflet of Medicinal Products for Human Use** Eudralex 3BC7A

**Guideline on pharmaceutical development of medicines for paediatric use** EMA/CHMP/QWP/805880/2012 Rev. 2

**REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION**
London, 28 July 2006 EMEA/CHMP/PEG/194810/2005

**HANDBOOK OF PHARMACEUTICAL EXCIPIENTS**

# ABOUT THE NEED FOR TAILORED PAEDIATRIC FORMULATIONS

## DOSE INACCURACY DUE TO INACCURATE MANIPULATION
## Pharmacokinetics of Lopinavir/Ritonavir in children

Administration of crushed 200mg/50mg Lopinavir/Ritonavir (Kaletra) tablets to children resulted significantly reduced Lopinavir and Ritonavir exposure with a decrease in AUC of 45 and 47% respectively as compared to whole tablets.

- The tablet formulation helps ensure solubility in the gastrointestinal tract and thus facilitates absorption. Disruption of the extrude matrix environment may adversely impact this formulation affect.
- The crushing of the pill leaves part of the drug(s) on the walls of the container or crushing device, and the transfer of the crushed substance to the food or liquid for mixing may also generate loss of the active drug.

Best and alt., Pharmacokinetics of Lopinavir/Ritonavir crushed vs. whole tablets in children", J. Acquir. Imm. Defic. Syndr., 58:385-391 (2011)

### Film-coated tablets: 200 mg lopinavir and 50 mg ritonavir

**Swallow KALETRA tablets whole. Do not chew, break, or crush KALETRA tablets.**

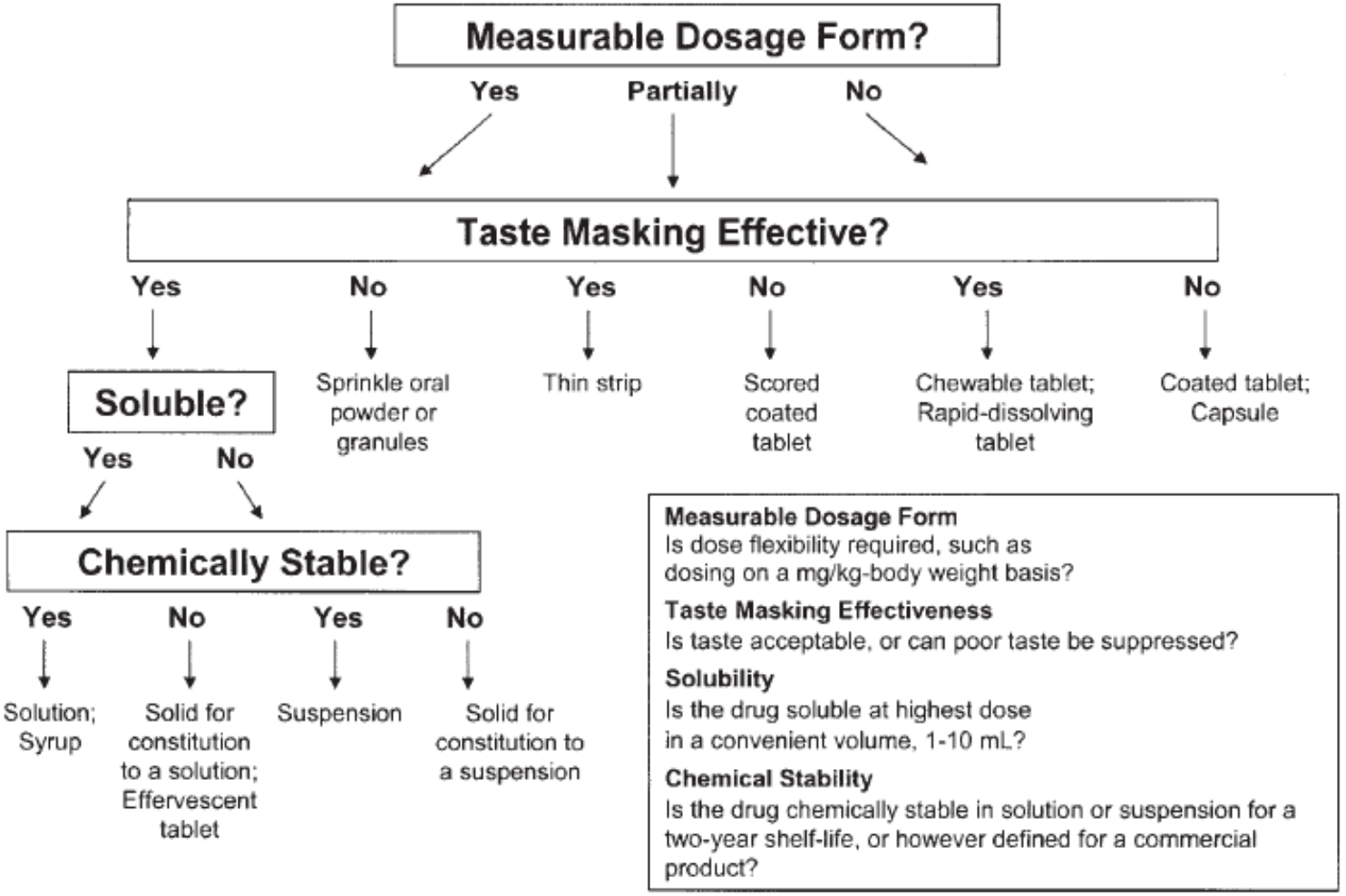
### Film-coated tablets: 100 mg lopinavir and 25 mg ritonavir

**Before prescribing KALETRA 100/25 mg tablets, children should be assessed for the ability to swallow intact tablets.** If a child is unable to reliably swallow a KALETRA tablet, theKALETRA oral solution formulation should be prescribed.

### Oral solution: 80 mg lopinavir and 20 mg ritonavir per mL

**KALETRA oral solution contains 42.4% (v/v) alcohol and 15.3% (w/v) propylene glycol.** Ingestion of the product over the recommended dose by an infant or a young child could result in significant toxicity and could potentially be lethal.

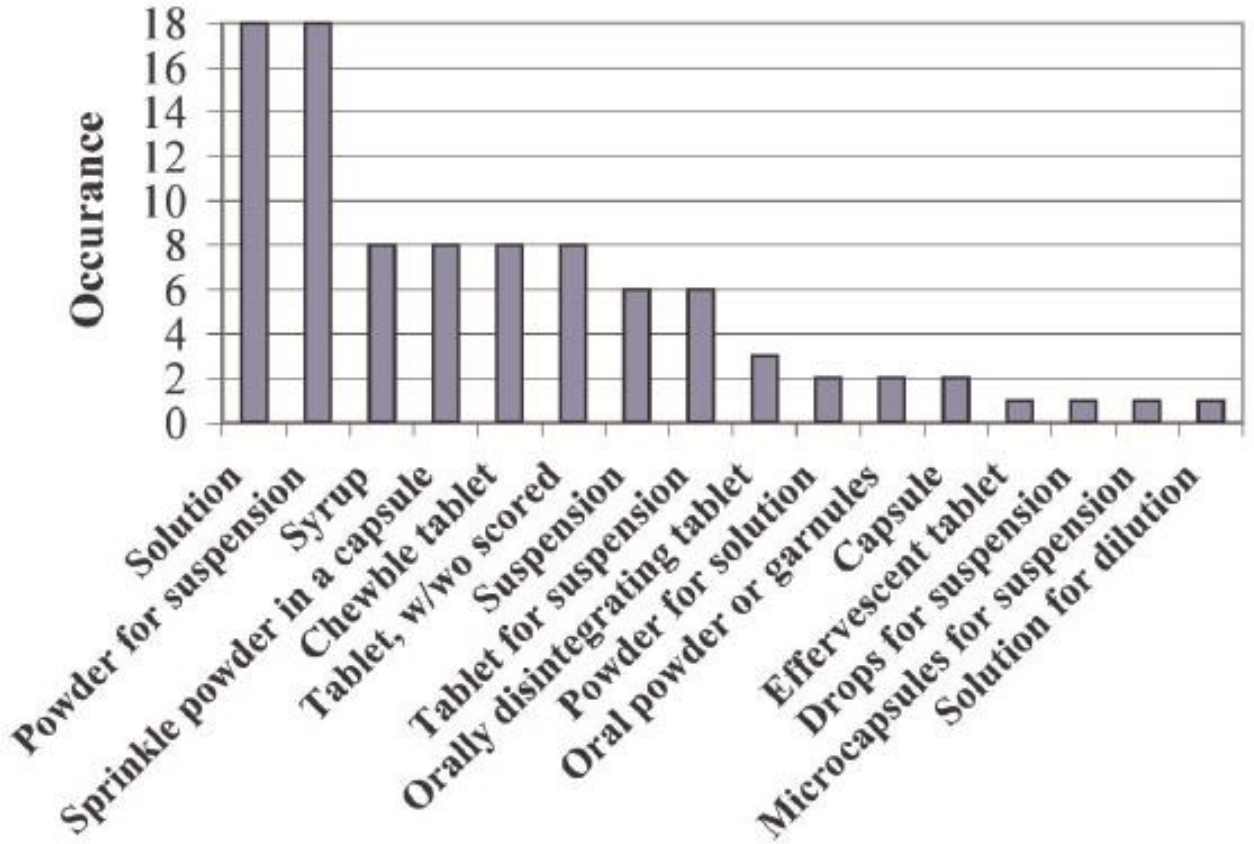
# Decision-making flow-chart in the choice of a paediatric oral formulation




JOURNAL OF PHARMACEUTICAL SCIENCES,
VOL. 97, NO. 5, MAY 2008

# Marketed oral paediatric formulations (1)

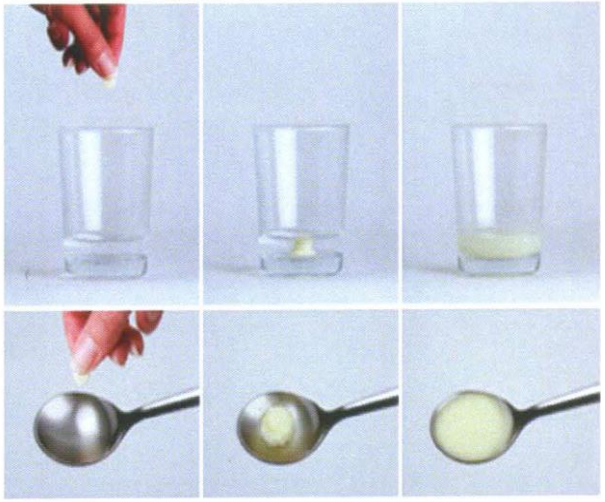
**US commercially available oral paediatric formulations (Physician's Desk Reference 2007)**




JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 97, NO. 5, MAY 2008

# Marketed oral paediatric formulations (2)

**Dispersible , soluble , effervescent preparations**



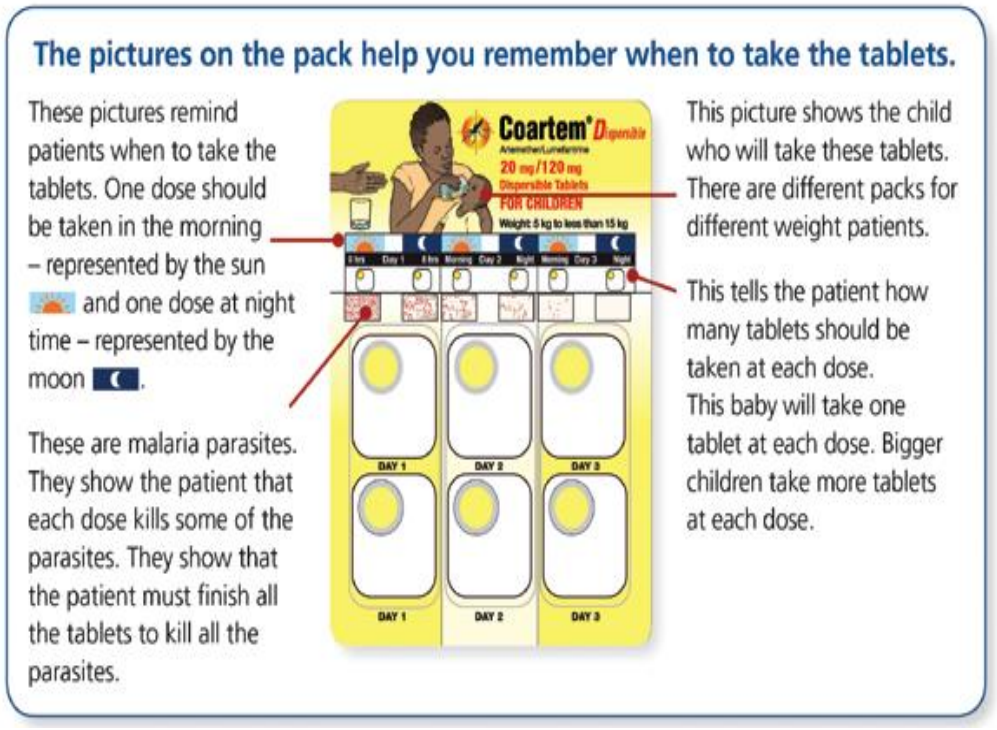
**Coartem® *Dispersible*** tablets
the first paediatric dispersible ACT (artemisinin-based dispersible combination therapy) developed especially for children with malaria, delivered to 50 malaria-endemic countries since launch in 2009

***Coartem Dispersible* is a sweet-tasting cherry-flavoured tablet that disperses in a small amount of water and is especially developed for and well accepted by children**.

• Round, flat, and yellow dispersible tablet each containing 20 mg of artemether and 120 mg of lumefantrine.

•The other ingredients are ……, crospovidone ….

•Place the Coartem/Riamet Dispersible tablets in a small amount of water **(approximately 10 mL per tablet)** in a cup. Allow the tablet(s) to disintegrate and stir gently before giving the solution to your child to drink. Afterwards, immediately rinse the cup with an additional small amount of water (approximately 10 mL) and give it to your child to drink completely.



# Marketed oral paediatric formulations (3)

## Orodispersible formulations

- **Can include Tablets (ODT) and thin Oro Dispersible Films (ODF)**
- **Intended to be placed directly in the mouth where they rapidly disintegtrate in saliva, usually within seconds, thus surpassing the need to swallow and the need of water.**
- **Suitable for soluble API. Limited in drug loading. Dose flexibility is limited.**
- **Taste masking essential**
- **Moisture sensitive: beware of the packaging**

CLARINEX RediTabs
**(desloratadine)**

**Place CLARINEX RediTabs tablet on your tongue and allow it to dissolve before swallowing.**

**Take your CLARINEX RediTabs tablet right away after opening the blister.**

**Adults and Adolescents 12 Years of Age and Over:**
- CLARINEX Tablets - one 5 mg tablet once daily **or**
- CLARINEX RediTabs Tablets - one 5 mg tablet once daily **or**
- CLARINEX Oral Solution - 2 teaspoonfuls (5 mg in 10 mL) once daily

**Children 6 to 11 Years of Age:**
- CLARINEX Oral Solution - 1 teaspoonful (2.5 mg in 5 mL) once daily **or**
- CLARINEX RediTabs Tablets - one 2.5 mg tablet once daily

**Children 12 Months to 5 Years of Age:**
- CLARINEX Oral Solution - 1/2 teaspoonful (1.25 mg in 2.5 mL) once daily

**Children 6 to 11 Months of Age:**
- CLARINEX Oral Solution - 2 mL (1 mg) once daily

# Marketed oral paediatric formulations (4)

## Chewable preparations

- **Can include chewable tablets and medicated chewing-gum (mainly OTC vitamins products)**
- **Tablets: intended to be chewed before being swallowed**
- **Medicated chewing gum: close resemblance to confectionery may limit their safe use**

**AMOXIL (amoxicillin)**

- Capsules of AMOXIL
- **Chewable Tablets of AMOXIL**

Each strength of the suspension of AMOXIL is available as a chewable tablet for use by older children.

- AMOXIL for Oral Suspension
- Pediatric Drops of AMOXIL for Oral Suspension

**SINGULAIR (montelukast sodium)**

**Tablets, Chewable Tablets, Oral Granules**

Dosage (by age) (2):

- 15 years and older: one 10-mg tablet.
- 6 to 14 years: one 5-mg chewable tablet.
- 2 to 5 years: one 4-mg chewable tablet or one packet of 4-mg oral granules.
- 6 to 23 months: one packet of 4-mg oral granules.

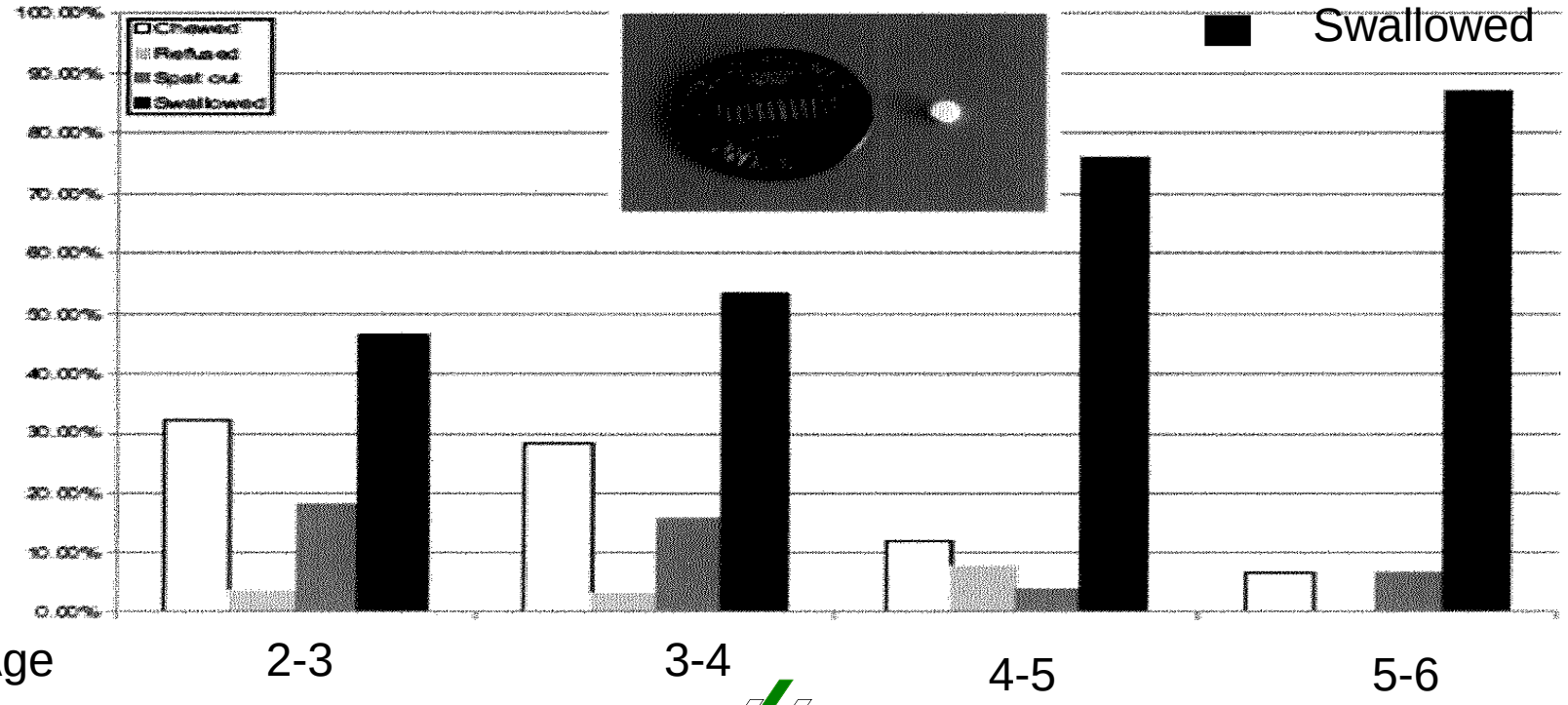
# Other oral paediatric formulations

## Minitablets

- **Defined as tablets with a diameter < 4mm (WHO)**
- **Small tablets containing a fraction of the required dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets.**

- Small tablets (3 to 5 mm diameter) are not acceptable for children below the age of 2
- Medium size tablets (5 to 10 mm diameter) are not acceptable for children below the age of 6 years
- Large Tablets (10 to 15 mm diameter) are not acceptable for children below the age of 12 years
- Very large tablets ( 15 mm and more) are not acceptable for children below the age of 18 years

Guideline on pharmaceutical development of medicines for paediatric use **(Draft)** EMA/CHMP/QWP/180157/2011




S. Thomson et. Alt, "Acceptability of 3mm minitablets in young children" , Pediatrics ,123:e235-238, 2009

# Parenteral administration (1)

Parenteral administration is the most commonly used route of administration for active substances for children who are seriously ill and for clinically unstable term and preterm neonates.

The route of intravenous administration (central or peripheral), site of injection, the injection volumes, the rate of administration, the viscosity, pH, buffering, osmolarity and, if relevant, the needle thickness and needle length should be described and justified.

The age and weight of the child, the maximum number of injections per day and the duration per treatment should also be discussed.

The volume should be justified according to the age of the children in the target age group(s). Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml, however lower volumes are warranted for neonates and infants.

Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment period.

# Parenteral administration (2)

IV: the daily allowance of fluid for paediatric patients receiving intravenous therapy is related to age and weight. For example, a 1 kg neonate may only receive 150 ml per day to include all nutritional requirements as well as therapy.

| Body weight | Volume per 24 hours |
|---|---|
| Less than 3 kg | 150 ml/kg<br>(but starting at 40-60 ml/kg for newborn) |
| 3-10 kg | 100 ml/kg |
| 11-20 kg | 1000 ml plus 50 ml/kg for each kg from 11-20 kg.<br>e.g. 15 kg = 1000 + (5x50) = 1250 ml |
| Greater than 20 kg | 1500 ml plus 20 ml/kg for each kg above 20 kg<br>e.g. 30 kg = 1500 + (10x20) = 1700 ml |
| Adult female | 2000 ml |
| Adult male | 2500 ml |

IM and SC: normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml, however lower volumes are warranted for neonates and infants

# Parenteral administration (3)

**High concentrated vials for intravenous administration compared to doses usually administered to neonates.**

| Active agent | Available concentration | Reference doses | Preterm, 1.5 kg | Term, 3 kg |
|---|---|---|---|---|
| Amikacin, adult vial | 500 mg/2 mL | 15-20 mg/kg | 130 mg, 0.12 mL | 50 mg, 0.2 mL |
| Amikacin, pediatric vial | 100 mg/2 mL | 15-20 mg/kg | 30 mg, 0.6 mL | 50 mg, 1.0 mL |
| Enoxaparin | 40 mg/0.4 mL | 1 mg/kg | 11.5 mg, 0.015 mL | 13 mg, 0.03 mL |
| Erythromycin | 1000 mg/20 mL | 5-10 mg/kg | 12 mg, 0.24 mL | 25 mg, 0.5 mL |
| Fentanyl[1] | 100 μg/2 mL | 1-3 μg/kg | 13 μg, 0.06 mL | 16 μg, 0.12 mL |
| Insulin | 300 U/3 mL | 0.1-1 U/kg per hour | 10.3 U, 0.03 mL | 10.6 U, 0.06 mL |
| Midazolam | 15 mg/3 mL | 0.1 mg/kg | 10.15 mg, 0.03 mL | 10.3 mg, 0.06 mL |
| Paracetamol | 500 mg/50 mL | 10 mg/kg | 15 mg, 1.5 mL | 30 mg, 3 mL |
| Phenobarbital | 200 mg/1 mL | 5 mg/kg | 17.5 mg, 0.0375 mL | 115 mg, 0.075 mL |
| Propofol | 200 mg/20 mL | 1-3 mg/kg | 2 mg, 0.2 mL | 4.5 mg, 0.45 mL |
| Ranitidine | 50 mg/2 mL | 0.5-1 mg/kg | 11.5 mg, 0.06 mL | 13 mg, 0.12 mL |

Formulations were sorted alphabetically and reported as available in Belgium, not necessary reflecting the setting in another country. A dose in a 1.5 and 3 kg newborn has been used for illustrative purposes. [1]Initial volumes ⩽ 0.2 mL.

**Due to the large difference in concentration, consecutive dilution and associated dose inaccuracy are more likely.**


•Parshuram CS, To T, Seto W, et al. Systematic evaluation of errors occurring during the preparation of intravenous medication. CMAJ 2008;178:42–8

•Uppal N. et alt. (2011) Drug formulations that require less than 0.1 ml stock solution to prepare dose for infant and children. CMAJ 183:E246:E248

• Karel Allegaert, “Neonates need tailored drug formulations”, World J Clin Pediatr. Feb 8, 2013; 2(1): 1–5.


# Design of a Paediatric Dosage Form (1)

Development pharmaceutics; formulation and manufacturing plan

**Define API(s) and dosage regime**

**Consider - route of administration**
**- suitable dosage form**

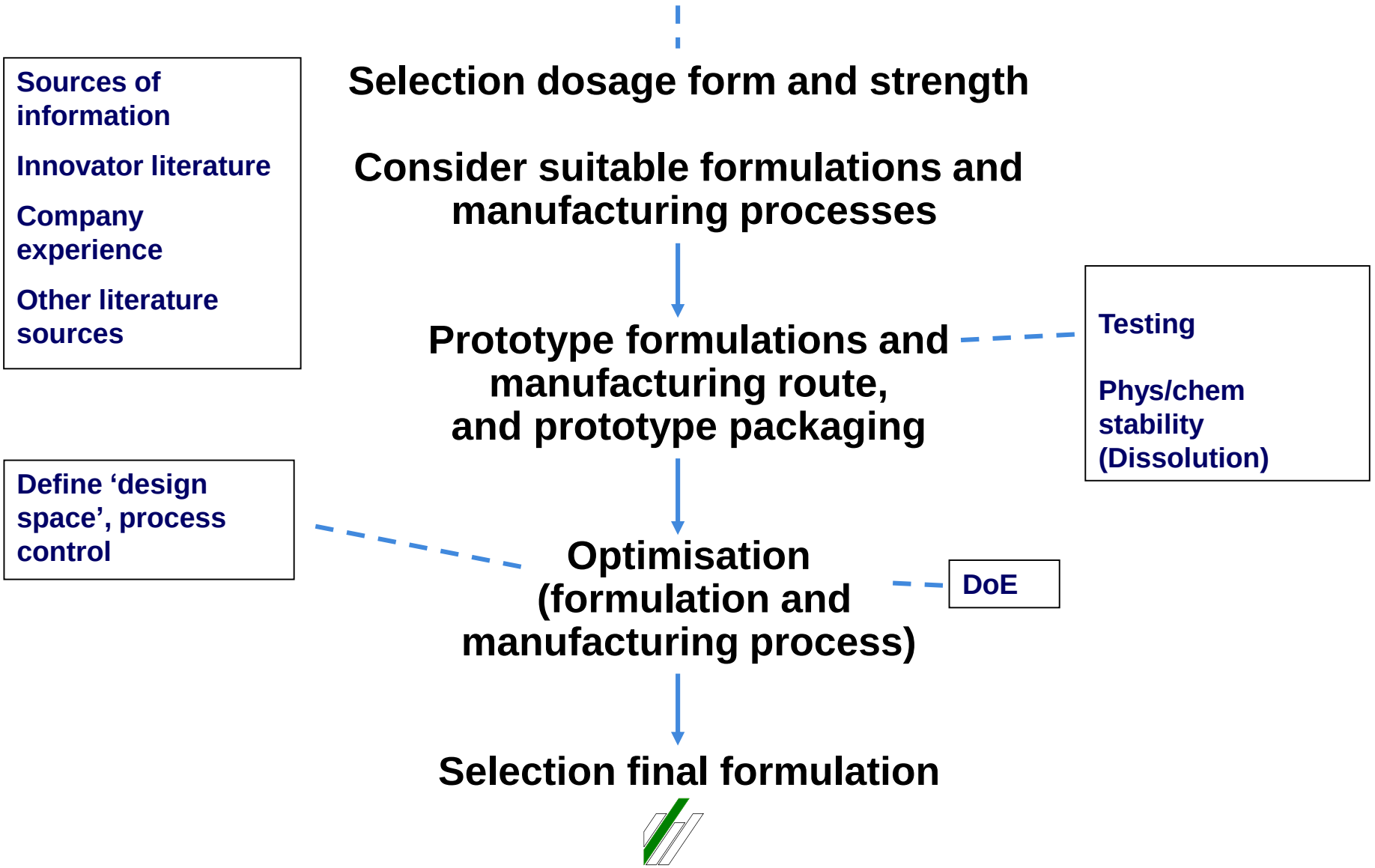
**What are pharmacokinetic characteristics of API(s)?)**
- **$t_{50}$, $C_{max}$, AUC**
- **BCS (for oral products**

**Determine relevant properties of API(s)**

**- physicochemical, crystallographic**
**- stability under 'stress'conditions**
**- compatibility with second API and/or common excipient**

- **Select dosage form and strength**

# Design of a Paediatric Dosage Form (2)



# Design of a Paediatric Dosage Form (3)

**Process scale-up studies/batches**
**Confirmatory stability (dissolution) studies**

↓

**Select final formulation, manufacturing process and packaging**

↓

**Registration stability batches**

↓

**Documentation for registration dossiers**

BE study to be considered if registrative clinical studies are not performed with final formulation and/or with product from different mfg. process

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*…… CIAO  DIDI ……*

*Thank you for your kind attention*

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