

# AGE-APPROPRIATE AND ACCEPTABLE PAEDIATRIC DOSAGE FORMS: MAKING MEDICINES CHILD SIZE



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# DISCLOSURES

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THE VIEWS AND OPINIONS EXPRESSED IN THIS PRESENTATION ARE THE AUTHOR'S OWN AND DO NOT REFLECT THE VIEW OF UCSF OR ACTELION.

THE AUTHOR HAS NO FINANCIAL OR OTHER CONFLICTS OF INTEREST TO REPORT.

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# IN THE PAST.....

When children were considered small adults

# BEFORE PAEDIATRIC REGULATORY LEGISLATION

## LACK OF FINANCIAL INCENTIVES AND CLINICAL STUDIES IN CHILDREN LED TO THE MAJORITY OF MEDICINES BEING DEVELOPED FOR ADULTS BUT STILL PRESCRIBED TO CHILDREN (1960S TO 2000S)

- ▶ Unlicensed - medicines that are used outside the terms of their license or which have no license for use.
- ▶ Off-label – licensed medication used in a different manner to that recommended in the license.
- ▶ A meta analysis of 33 studies found the percentage of children who received at least one off-label and/or unlicensed drug ranged from 42.0 to 100 %, with newborns being the population that received most of such drugs<sup>1</sup>.
- ▶ Numerous studies demonstrating **adverse drug reactions, dosing errors** and **non-compliance** have been linked to unlicensed or off-label drug use of adult licensed medications in paediatric patients<sup>2</sup>.



# BEFORE PAEDIATRIC REGULATORY LEGISLATION

## WHAT WERE THE COMMON ISSUES IN PAEDIATRIC PATIENTS WHEN ONLY ADULT SIZED DOSAGE FORMS EXISTED?

Route of Administration	Dosage Form	Characteristic & Related Issue for Paediatric Patients
Oral	Tablets & Capsules	<p>Size - Swallowability</p> <p>Dose Strength - Typically too high with fixed strength</p> <p>Excipients - Concentrations not tolerated / unknown Tox profile</p> <p>Packaging – No child resistant features</p>
Parenteral	Injections & Infusions	<p>Dose Volume - Too high or too low (accuracy for dispensing)</p> <p>Dose Strength - Typically too high</p> <p>Excipients - Concentrations not tolerated / unknown Tox profile</p> <p>Administration Site - Painful administration</p>
Inhalation	Dry Powder Inhalers, Nebulisers, & Pressurized Metered Dose Inhalers	<p>Device - Ability to coordinate inhalation with device activation, long administration time</p> <p>Dose Strength - Typically too high with fixed strength</p> <p>Excipients - Concentrations not tolerated / unknown Tox profile</p>
Transdermal	Creams, Ointments & Gels	<p>Dose Strength - Typically too high with fixed strength</p> <p>Administration Site - Tolerability from API / Excipients (local &amp; systemic)</p> <p>Excipients - Concentrations not tolerated / unknown Tox profile</p>



# BEFORE PAEDIATRIC REGULATORY LEGISLATION

## WHAT WAS DONE TO ENABLE ADULT DOSAGE FORMS TO BE USED BY PAEDIATRIC PATIENTS?

- ▶ **Modify / manipulate adult dosage form<sup>3</sup>**
  - Crush tablet / open capsule and add dosing vehicle to prepare liquid preparation
  - Crush tablet / open capsule and add to soft food
  - Split tablet into segments to enable swallowability or appropriate dose strength
  - Dilute parenteral preparation to produce lower strength
  - Adjust infusion rate / infusion volume of infusion preparation
  - Use spacers / face mask with inhalation device
  - Extemporaneous preparation for nebulization



# BEFORE PAEDIATRIC REGULATORY LEGISLATION

## WHAT WAS DONE TO ENABLE ADULT DOSAGE FORMS TO BE USED BY PAEDIATRIC PATIENTS?

- ▶ Manufacture “gold standard” oral liquid preparation

**Solubility** – solvents, surfactants, pH modifiers

**Suspendability** – pH modifiers, suspending / dispersing agent, antifoaming agents

**Microbial Stability** – pH modifiers, preservatives, sugars (>80% w/v)

**Chemical Stability** – pH modifiers



**Palatability** – Sugars, sweeteners, flavouring agents, colouring agents

**Dosing Device** – Spoon, syringe, dosing cup, nasal gastric tubing, dropper

**Shelf Life** – refrigeration , reconstitution from powder

**Ease of use** – Bulky, difficult administration on the go



# BEFORE PAEDIATRIC REGULATORY LEGISLATION

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## WHAT WAS DONE TO ENABLE ADULT DOSAGE FORMS TO BE USED BY PAEDIATRIC PATIENTS?

- ▶ **Orange flavour incorporated into an antibiotic suspension contains:**

Acetone, maltodextrin,  $\alpha$ -tocopherol-acetaldehyde, modified starch, anisaldehyde, monomethyl succinate,  $\beta$ -Caryophyllen, orange aldehydes, n-butyric acid, orange oil FLA CP, butylbutyryl lactate, orange oil Valencia 2X, decalactone- $\delta$ , orange oil 5X Valencia, dimethyl benzylcarbacetate, orange essence oil, ethylalcohol, orange fruit ketones, ethylbutyrate, orange terpens, ethylmaltol, peppermint oil, ethyl vanillin, propylen glycol, furaneol, tangerine oil, grapefruit terpens, vanille extract, heliotropin, and water

- ▶ **Prescribed to paediatric patients across all age ranges**

# BEFORE PAEDIATRIC REGULATORY LEGISLATION

## WHAT WAS (*AND STILL IS*) DONE TO ENABLE ADULT DOSAGE FORMS TO BE USED BY PAEDIATRIC PATIENTS?

### ▶ .....the other tricks

- Reward / Bribe (e.g. sweets, treats, iPad time, etc)
- Conceal (e.g. food, beverages, sugar) & deceive (e.g. administer whilst asleep)
- Greater involvement in self medication (How? When? Where?)
- Create a fun and creative way for administration
- Educate and train
- Be open, honest & positive
- Administer by someone not the parents
- ...and when all else fails threaten (remove treats), hold down, take to hospital/doctor



# WITH THE INTRODUCTION OF PAEDIATRIC LEGISLATION

The rise of paediatric formulation development

USA - 1997 Best Pharmaceuticals for Children Act & 2003 Pediatric Research Equity Act

EU - EU Legislation 2006/1901; effective since January 2007

# PAEDIATRIC DRUG PRODUCT DEVELOPMENT

## DEVELOPING A “PAEDIATRIC QUALITY TARGET PRODUCT PROFILE”

..... product design created by an **interdisciplinary team**, providing the opportunity for detailed discussion of the **disease state**, **therapeutic goals**, **target population** and **special requirements** in conjunction with traditional drug product quality requirements



### ▶ Safety

- Dose API
- Excipients
- Medication Errors

### ▶ Dose

- Device
- Flexibility
- Accuracy

### ▶ Acceptability

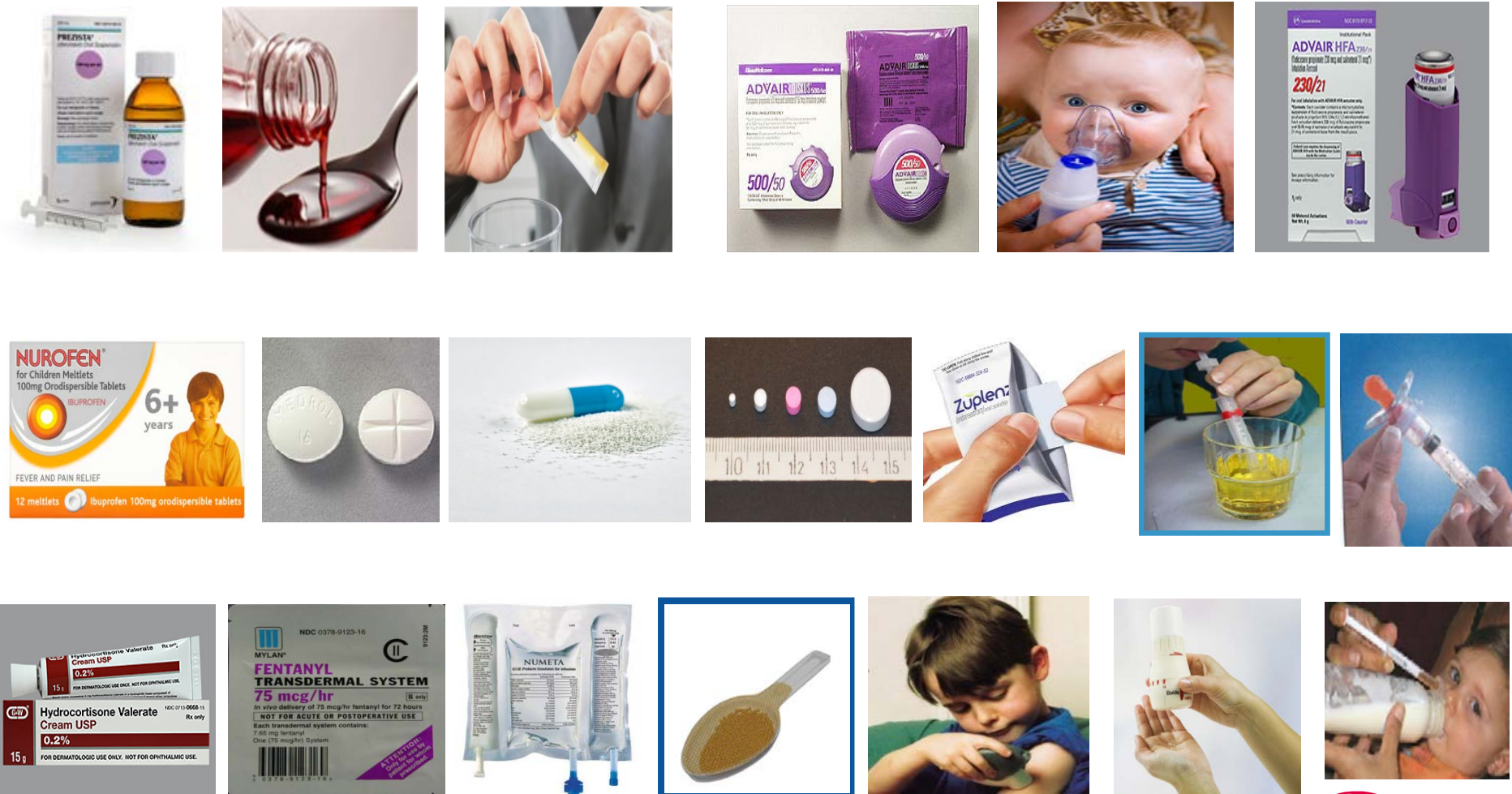
- Size
- Volume
- Taste
- Treatment Regimen
- Practical Handling

### ▶ Also consider

- Parents / Carer
- Healthcare Professionals
- Teachers

# PAEDIATRIC DRUG PRODUCT DEVELOPMENT

## AGE-APPROPRIATE PAEDIATRIC DOSAGE FORMS / DEVICES





# PAEDIATRIC DRUG PRODUCT DEVELOPMENT

## AGE-APPROPRIATE PAEDIATRIC DOSAGE FORMS

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	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
<b>Nasal</b>							
	Solution	3	4	4	4	4	4
	Semisolid DF	2	3	3	4	4	4
<b>Rectal</b>							
	Suppositories	4	5	5	4	3	2
	Rectal Enema	5	4	4	3	3	2
	Rectal capsules	2	3	4	4	4	3
<b>Topical/ transdermal</b>							
	Ointment, Cream, Gel	4	4	4	5	5	5
	Liquid DF	4	4	4	5	4	4
	Transdermal Patch	1	2	2	4	4	5
<b>Parenteral</b>							
	i.v. Solution	5	4	4	4	4	3
	i.m.	3	3	3	4	4	3
	s.c.	4	4	4	4	4	3
	Pump system	5	4	4	4	4	3
<b>Pulmonary</b>							
	Nebuliser	2	3	4	5	4	3
	MDI / Spacer	1	3	4	5	4	4
	DPI	1	1	3	4	5	5
<b>Ocular</b>							
	Eye drops	3	4	4	4	5	5
	Semisolid DF	2	3	4	4	4	4

\*DF: Dosage Forms

### Table Key

	Early ages (applicability)	Higher ages (preference of children)
1	not applicable	not accepted
2	applicable with problems	accepted under reserve
3	probably applicable but not preferred	acceptable
4	good applicability	preferred acceptability
5	best and preferred applicability	dosage form of choice

Guidance from the EMA<sup>4</sup>





# PAEDIATRIC DRUG PRODUCT DEVELOPMENT

## NEONATES – SPECIAL CONSIDERATION AMONGST PAEDIATRIC PATIENTS

*“A SOCIETY WILL BE JUDGED ON THE BASIS OF HOW IT TREATS ITS WEAKEST MEMBERS” POPE JOHN PAUL II*



- ▶ The ADME properties of a drug differs greatly in newborns from other infants and children across the various routes of administration<sup>5</sup>.
- ▶ A specific neonate drug product may need to be developed for this age range.
- ▶ Parenteral administration is considered most optimal<sup>6</sup>
  - Osmolarity
  - Electrolytes
  - Dose volume / infusion rate
  - Strength
  - Excipients
  - Dose preparation (dilution / reconstitution)



# CASE STUDY

## CASE STUDY

Disease Area	Respiratory
Indication	Asthma
Development Phase (Clinical Phase I to IV)	Ph1
Estimated paediatric dose range	TBD. Initial estimate 10 – 1200 mg
Route of administration (oral, IV, IM, SC, etc)	Oral (immediate release)
Target paediatric age range	1 year to 18 years
Dosing frequency (daily, weekly, every x weeks, etc.)	Daily
Adult dosage form , available dose strengths & composition	Capsule for clinical development (wet granulation) Tablet for Ph3 and commercial (wet granulation) 50mg (8mm round) , 100mg (10 mm round) , 300mg (13 mm x 5.1 mm), 600mg (15 mm x 5.9 mm) Lactose, mannitol, sodium lauryl sulphate, colloidal silicon dioxide, crospovidone, magnesium stearate, OraMix film coat
Drug Substance properties: - OHB class - BCS class - Solid Form - Melting point - pKa - Solubility/pH solubility profile  - Log P - Log D - Stability (solid and liquid forms)	OEL 0.1–0.01 mg / m <sup>3</sup> (strict handling) II - Positive food effect demonstrated in Adults Crystalline free base 198 C 2.8 pH 2 – 0.01 mg/mL, pH 4.5 – 0.01 mg/mL, pH 6.8 – 0.001 mg/mL, SGF – 0.01 mg/mL, FaSSIF – 0.1 mg/mL, FeSSIF – 1.00 mg/mL 2.8 2.6 Good bulk stability. Poor aqueous stability at 1 week / room temperature

# CASE STUDY

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## CASE STUDY

### ► Considerations for Dosage Form Selection

- Can adult tablets be used by adolescent patients?
  - Size – justification from literature / previous marketed products and acceptability study in clinical trials
  - Strength – do the adult strengths fit the adolescent dose regime? – input from clinical team and modeling & simulation required.
  - Excipients – Check safety in literature / previous marketed products
  - Food effect – add food effect study in clinical trials.
- Ready-to-Use oral liquids may not be technically feasible due to poor aqueous stability
- Oral solution formulations are likely to be challenging due to poor aqueous solubility
- Chewable / orodispersible tablets may evoke a gritty mouth sensation due to low drug solubility in the mouth
- Taste assessment needs to be performed to understand whether taste masking is required and help guide dosage form selection
- Sprinkling multiparticulates onto food may cause positive food effect
- Can the granules used to make the adult capsules / tablets be used to make granules for a reconstitution preparation or mini tablets (check excipients safety, dose range achievable, in-use stability, technical feasibility e.g. minitableting, sachet filling)
- Mini tablets, granules for reconstitution, dispersible tablets, tablets and capsules are promising dosage forms.

# PAEDIATRIC DRUG PRODUCT DEVELOPMENT

## LOOKING TO ADDRESS THE GAPS IN OUR KNOWLEDGE

..... R&D is being conducted across academia and the healthcare industry investigating the many areas of paediatric drug product development that currently provide challenges.

For example.....

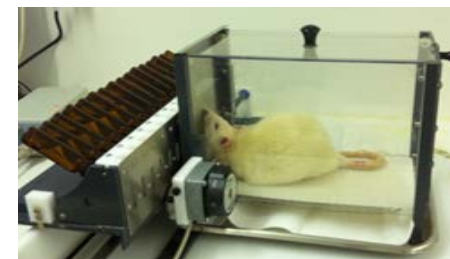
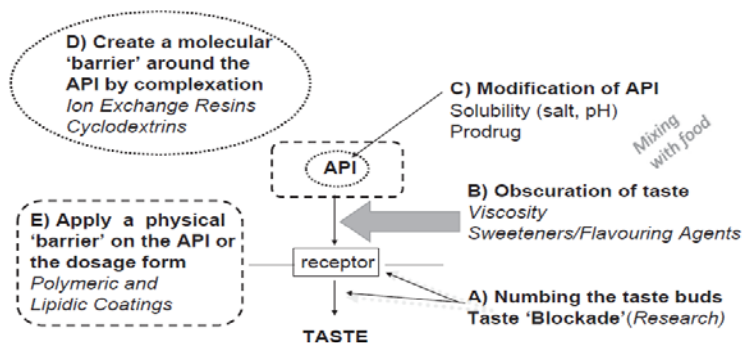
– **Acceptability of dosage forms across the paediatric age ranges**

- *Age-appropriate and acceptable paediatric dosage forms: Insights into end-user perceptions, preferences and practices from the Children's Acceptability of Oral Formulations (CALF) Study<sup>7</sup>*

– **Database of safety limits of excipients across the paediatric age ranges<sup>8</sup>**



– **Paediatric taste preferences with novel technologies for taste-masking with predictive evaluation methods<sup>9</sup>**



# PAEDIATRIC DRUG PRODUCT DEVELOPMENT

## LOOKING TO ADDRESS THE GAPS IN OUR KNOWLEDGE

- ▶ ..... Various Formulation Networks also exist....
- ▶ European Paediatric Formulation Initiative (EuPFI)
- ▶ United States Paediatric Formulation Initiative (USPFI)
- ▶ Global Research in Paediatrics (GRiP) Work Package 5 - Paediatric Formulations
- ▶ IQ Consortium Pediatric Working Group
- ▶ Pediatric Formulations Task Force (American Association of Pharmaceutical Scientists)
  
- ▶ Accelerating paediatric formulation development through smart design and predictive science
  - Research Councils UK / Innovate UK Funded Research
  - Astrazeneca, Pfizer, GSK, BMS, Juniper Pharma Services, University College London, Aston University, Academy of Pharmaceutical Sciences Leicester, University of Birmingham, University of Bath
  - Taste evaluation, Acceptability testing, Prediction of human exposure in children, Technology platforms for paediatric medicines

# SUMMARY

- Paediatric drug development is part of our daily pharmaceutical business
- Considering the age-appropriateness of the drug product to the specific patient population is vital.
- Technical difficulties exist for every molecule when developing a patient-centric dosage form.
- Excipient safety, dose accuracy / flexibility and palatability and all integral elements of pediatric medicines that need to be addressed with every drug product.
- Continued efforts are being made by academia and the healthcare industry to fill the gaps in our knowledge with scientific research



# THANK YOU.

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