FONDAZIONE PER LA RICERCA FARMACOLOGICA GIANNI BENZI ONLUS

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

XVI FORESIGHT TRAINING COURSE
Repurposing to cover unmet needs: the current scenario in Europe and the proposed changes to the Pharmaceutical Legislation

How can repurposing meet therapeutic needs in paediatrics?

Introduction to the round table

Viviana Giannuzzi

18 Dec 2023 - Bari, Italy

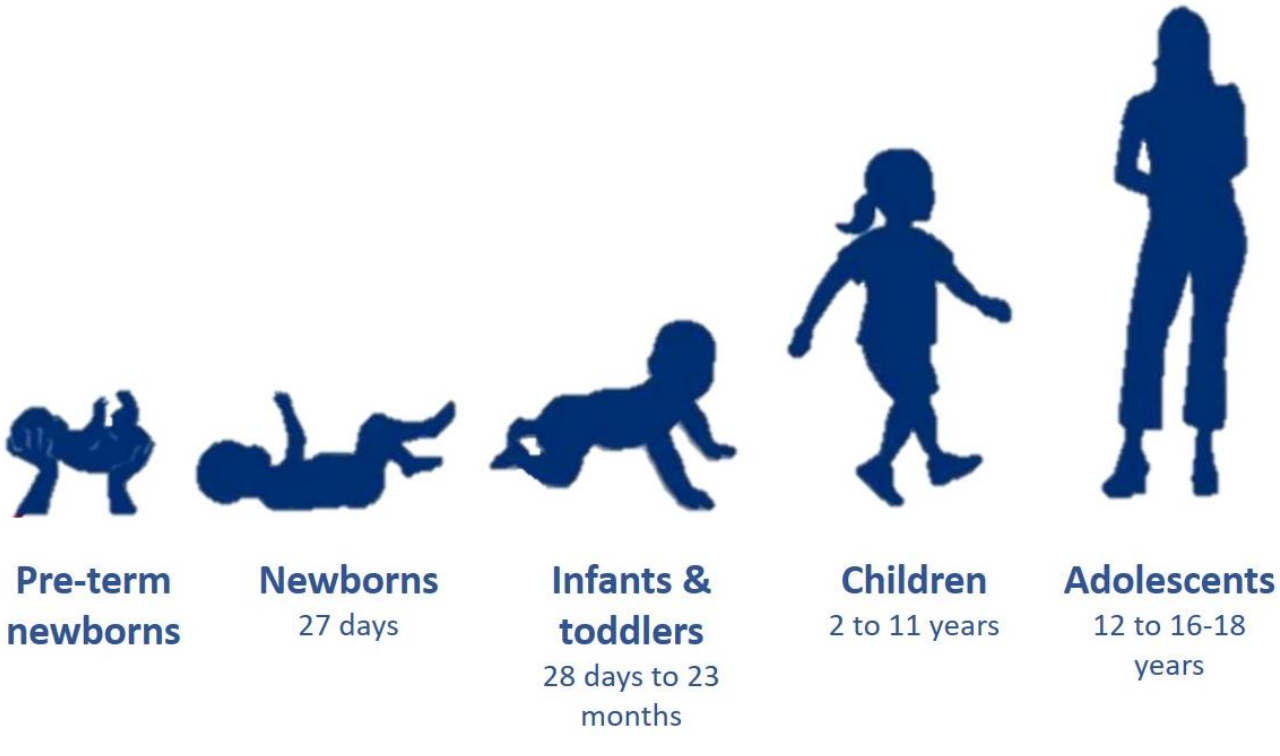
Disclaimer

The views expressed in this presentation are the personal views of the speakers

No financial disclosure to declare

Challenges in paediatric R&D

Clinical studies in children are more difficult and take longer



CPMP/ICH/2711/99

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Challenges in paediatric R&D

Regulatory requirements

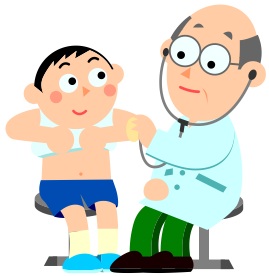
- ✓ GCP-ICH E11

Ethical concerns

- ✓ Children are vulnerable and unable to provide legal consent
- ✓ Concerns for enrolling children in trials
- ✓ Concerns for placebo
- ✓ Pain, discomfort, fear, distress to be minimized

Methodological

- ✓ Age-related differences in drug handling
- ✓ Few patients
- ✓ Sample as small as possible but sufficient statistical power necessary
- ✓ Need for age-appropriate formulations
- ✓ Alternative approaches necessary
- ✓ Unability to communicate adverse events
- ✓ Need for specific biomarkers



Multi-national studies

Jeopardized legal and ethical frameworks

Families

- ✓ Unfamiliar with trials
- ✓ Worries about risks of new treatments

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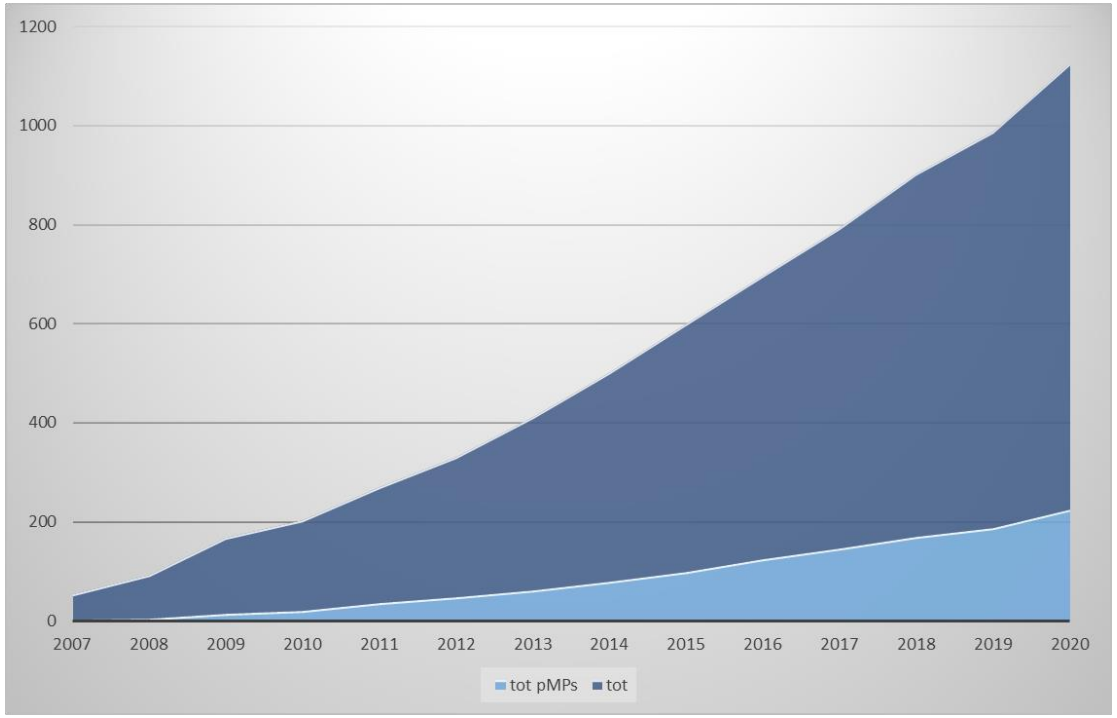
Paediatric drugs: current status

Posted interventional trials:

- in adults
  - 15.263 in 2013
  - 26.034 in 2023 *(Dec, 13)*
- in paediatric patients (~17%)
  - 2.661 in 2013
  - 4.497 in 2023 *(Dec, 13)*

clinicaltrials.gov

EU centrally authorised medicines for adults and children



European Public Assessment Reports and European Paediatric Medicines Database (e-PMD)

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Paediatric drugs: current status

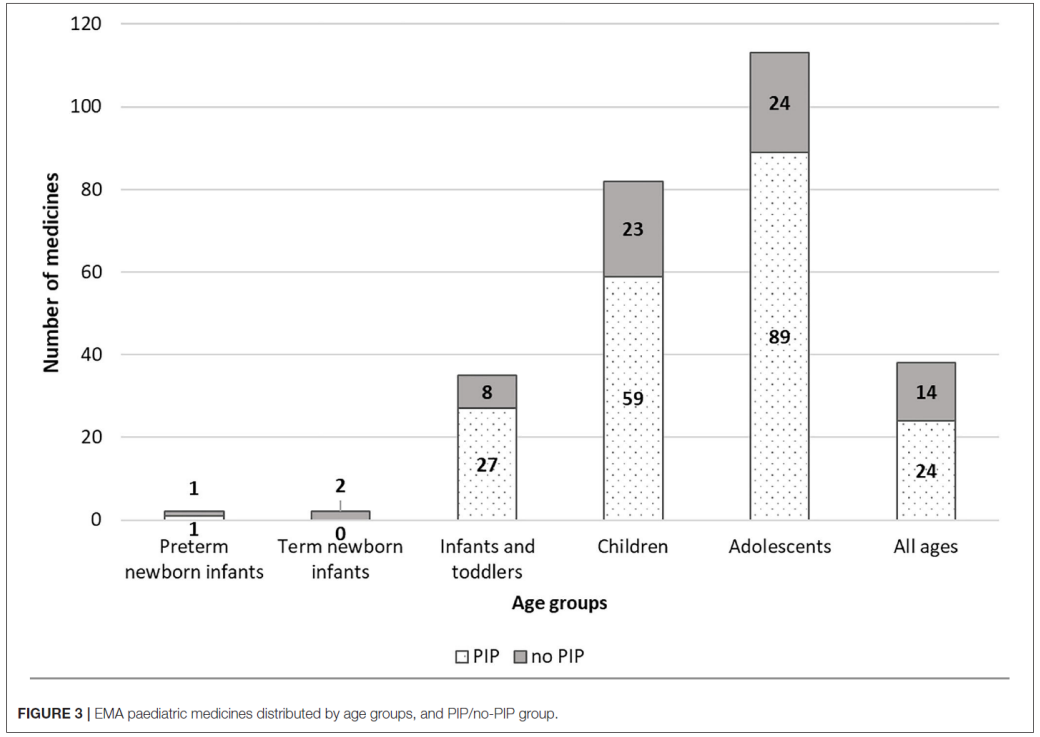

FIGURE 3 | EMA paediatric medicines distributed by age groups, and PIP/no-PIP group.

Toma et al, Front Med (Lausanne) 2020

- Less medicines for younger children
- ~90% of rare diseases can begin in childhood ⇨ 'children are orphan two times

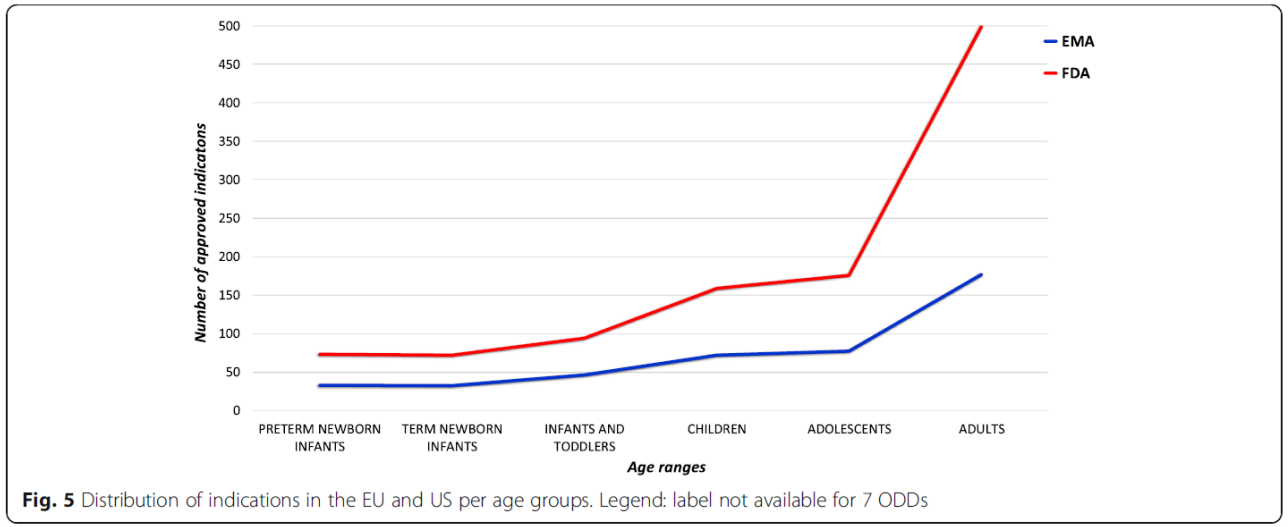

Fig. 5 Distribution of indications in the EU and US per age groups. Legend: label not available for 7 ODDs

Giannuzzi V et al. OJRD 2017

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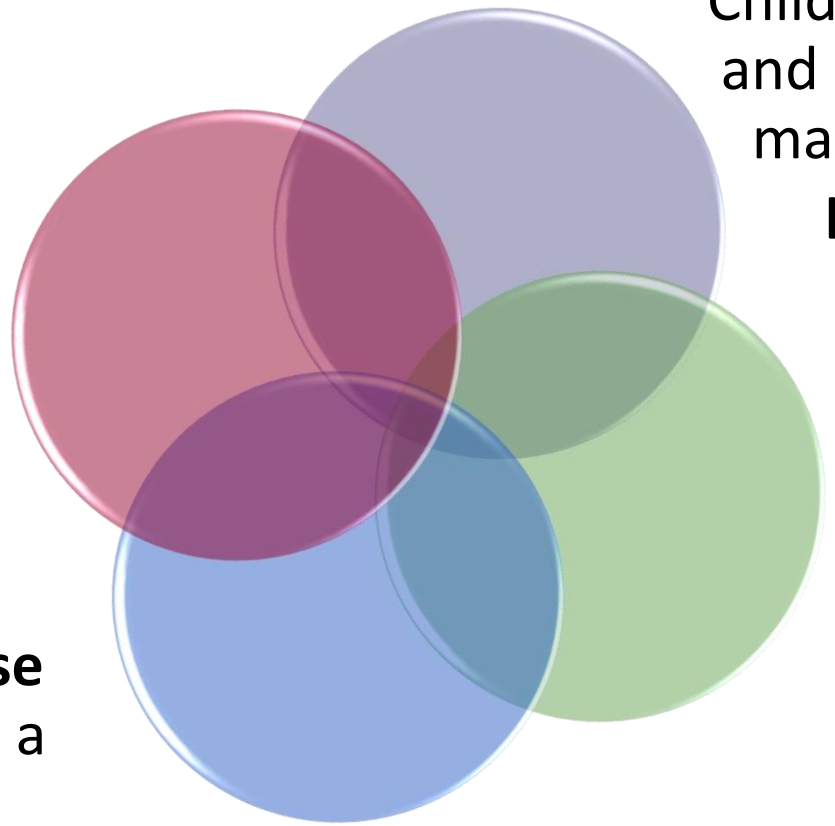
Paediatric drugs: current status

13-69% of the prescriptions within a paediatric hospital setting is **off-label** ⇨ percentage dramatically increases in neonatal setting



Children represent 20% of the (EU and US) population, but ~ 70% of marketed drugs have not been **properly tested** for them

Only 20% of medicines approved for a **rare disease** affecting also children has a paediatric indication

Paediatric drug development is usually **driven by adult-based development** and follows clinical trials in adults

Toma M et al Front.Med 2021; Nguengang WS et al. Eur J Hum Genet 2020; European Commission 2017 "Study on Off-Label Use of Medicinal Products in the European Union"; EuOrphan database update December 2020

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Off-label use to cover paediatric unmet needs

Off-label use:

"all paediatric uses of a marketed drug not detailed in the Summary of Product Characteristics" with particular reference to:

- therapeutic indication
- age
- strength (dosage by age)
- pharmaceutical form
- route of administration

- Does not necessarily mean off-evidence
- A source of data on medicine use in a specific indication, subset, etc.
- Possibility to explore new routes

- No information on effective and safe dosing regimens
- Possible manipulation of the dosage form to achieve the required dose
- Higher risk of medication errors
- Drug-drug interaction unknown
- Poor warnings on safety

Neubert A et al. Pharmacol Res. 2008

If an off-label use goes into a repurposing path…

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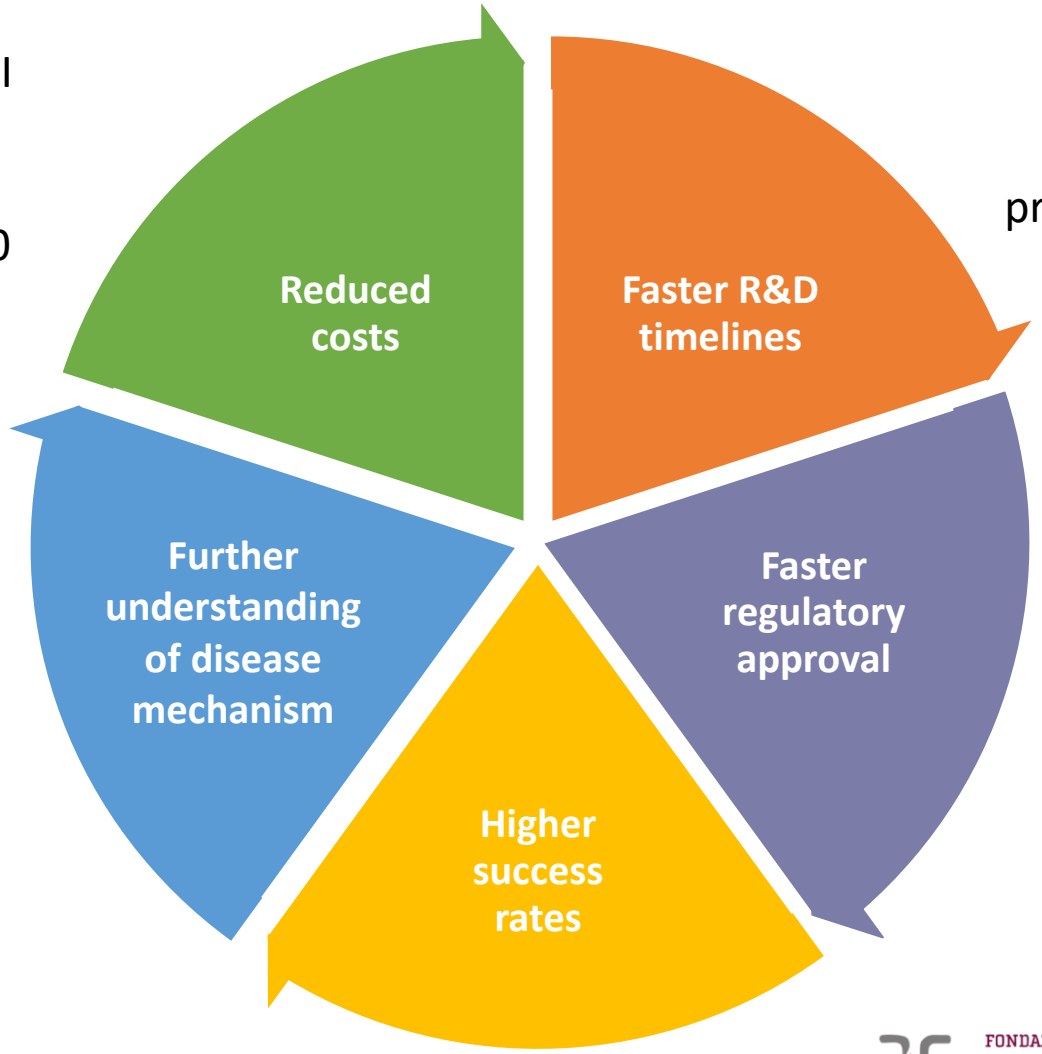
Paediatrics shares main advantages from repurposing…

much of preclinical and phase I/II work already done (It is estimated that repurposing a drug will cost an average of $300 million as opposed to $2–3 billion invested on a NCE)



Because of the availability of preclinical, safety and tolerability data

A repurposed drug may reveal new targets, pathways and biomarkers hitherto unknown in a disease

Since a repurposed drug already has a positive preclinical and safety data

Pushpakom, Springer 2022

also depending on the new indication and existing patent protection

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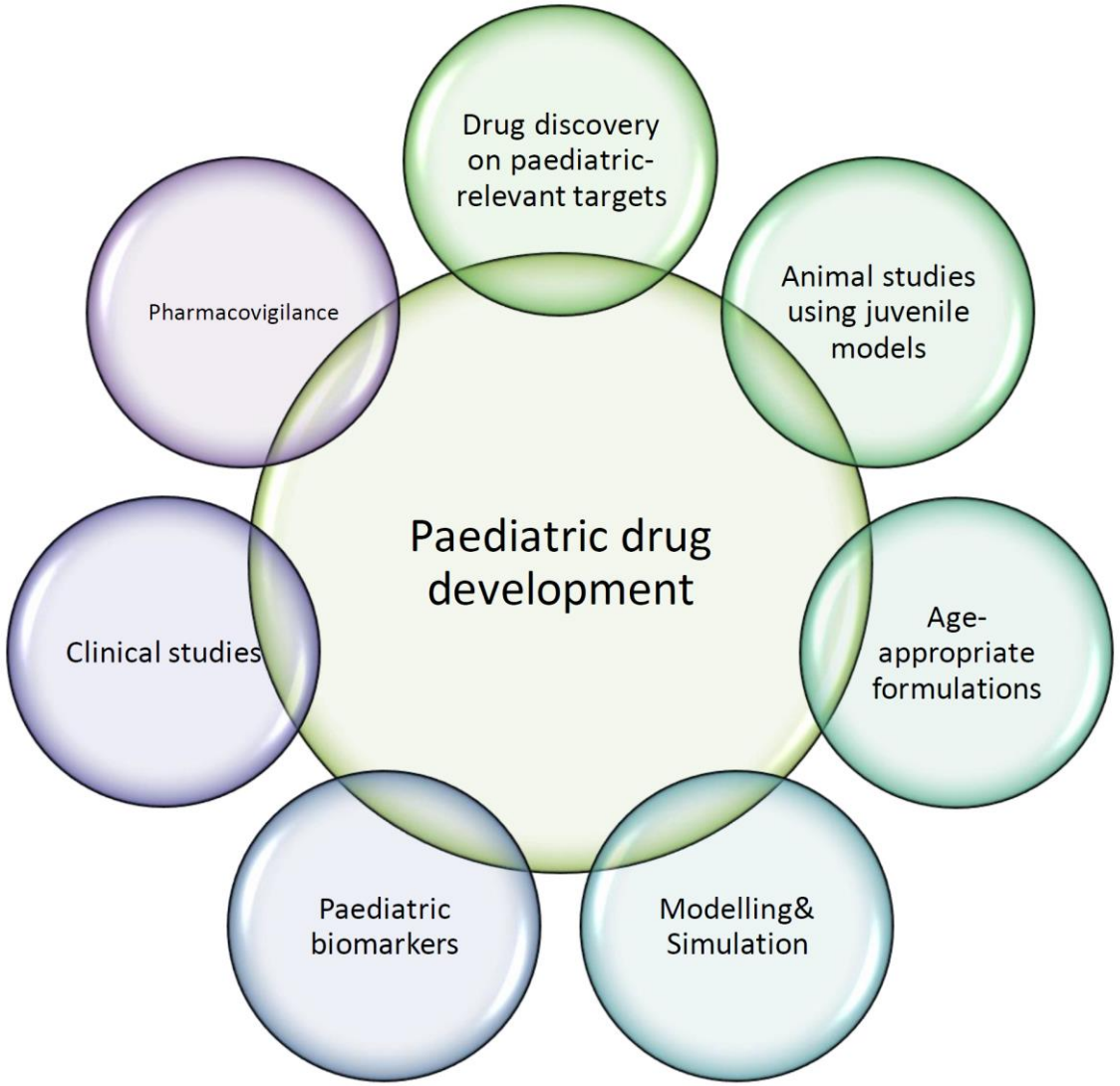
...still keeping the paediatric specificities..



Parts of the non-clinical and sometimes of the clinical evidence already available

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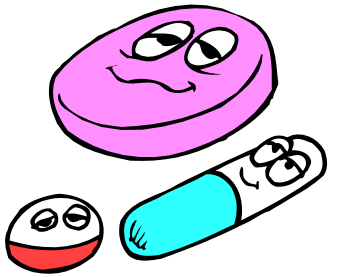
Age-specific process

DISEASE	TIMING OF STUDIES	TYPE OF STUDIES
1. Predominantly or exclusively affecting paediatric patients	The development program will be conducted in children, **even in the initial phases**	*ENTIRE PROGRAM:* PK/PD, efficacy, safety
2. Serious or life-threatening conditions occurring in both adults and paediatric patients, with no or limited therapeutic options	Paediatric development should begin **early**, **but following phase 1 in adults** and after potential benefit has been demonstrated	*IF **different*** indication and course of disease → *ENTIRE PROGRAM*: PK/(PD), efficacy, safety *IF **similar*** indication and course of disease → PK, safety
3. Other diseases or conditions	**At later phases** of clinical development Limited paediatric data available at the time of the application, but more would be expected after MA	PK, short and long term safety

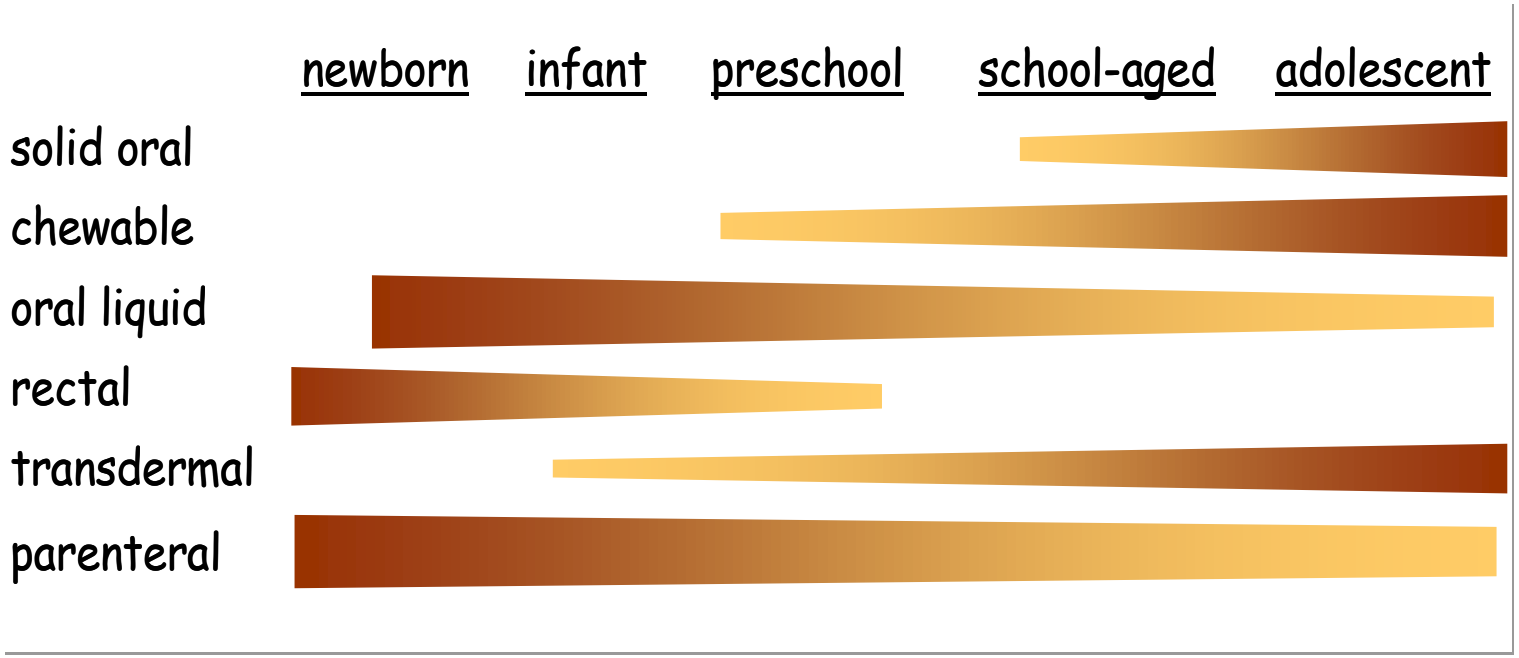
ICH Topic E11

Need for ad hoc formulations

- Excipients used in adults may be toxic in children
- The ability to use different dosage forms varies greatly



- influence of age and maturity
- influence of illness



★**Oral liquid formulations** (drops, syrups, solutions or suspensions prepared with powders or microgranules)

Successful examples on repurposed drugs but only few are also for paediatric use

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Marketed repurposed paediatric medicines

- **Sildenafil** approved in 1998 in US and in 2009 in EU for pulmonary hypertension children > 1 year (Revatio®)
- **Propranolol** approved in 1967 in US and in 2014 in EU for infantile haemangioma in children 5 weeks- 5 months (Hemangeol®/Hemangiol®)
- **Thalidomide** approved in 1998 in US for erythema nodosum leprosum children > 12 years (Thalomid®)

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Marketed repurposed paediatric medicines

Midazolam (Buccolam®)

- Oromucosal solution
- Epileptic seizures
- 3 months - < 18 years

Agreed PIP in 2009

Area	Number of studies	Description
Quality	1	Development age-specified pre-filled syringes
Non-clinical	-	Not applicable.
Clinical	1	Open label, single dose, pharmacokinetic study of oromucosal midazolam administered to children from 3 months to less than 18 years undergoing routine elective surgery.

MA in 2011

- 1 PK study
- In silico PBPK modelling
- Literature

EMEA-000395-PIP01-08; Buccolam EPAR

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Incentives for off-label paediatric medicines

20 EU-funded projects to study 24 off-patent active substances in paediatrics, develop and authorise for marketing new age-appropriate (oral or parenteral) formulations

Hybrid medicine for all paediatric ages

2 open-label trials

Paediatric formulation: granules

Project	Active Substance(S)	Addressed paediatric indication(s)	Therapeutic area
TINN	Ciprofloxacin*	treatment of infections in preterm and term newborns	Infections
	Fluconazole		
TINN2	Azithromycin	treatment of infections in preterm and term newborns	
NeoMero	Meropenem	treatment of late-onset sepsis in neonates and infants aged <3 months treatment of bacterial meningitis in neonates and infants aged <3 months	
NeoVanc	Vancomycin	treatment of late onset bacterial sepsis caused by vancomycin susceptible bacteria in neonates and infants aged under three months	
NeoOpioid	Morphine	treatment of acute pain	Pain
	Fentanyl		
GAPP	Gabapentin	treatment of chronic pain	
Loulla & Philla	Methotrexate*	treatment of Acute Lymphoblastic Leukemia	Malignant neoplasms
	6-Mercaptopurine*		
03K	Cyclophosphamide	treatment of paediatric malignancies	
	Temozolomide		
EPOC	Doxorubicin*	treatment of childhood cancer	
HIP trial	Dopamine	management of hypotension in preterm newborns	Cardiology
NeoCirc	Dobutamine	treatment of systemic hypotension in infants	
LENA	Enalapril	cardiac failure in children	
NEMO	Bumetanide	treatment of neonatal seizures in babies with hypoxic ischemic encephalopathy	Neurology
KIEKIDS	Ethosuximide	treatment of absence and myoclonic epilepsy	
TAIN	Hydrocortisone*	treatment of adrenal insufficiency in neonates and infants	Endocrinology
METFIZZ	Metformin	treatment of polycystic ovary syndrome	
CloSed	Clonidine*	Sedation in intensive care	Intensive care/anaesthesiology
DEEP	Deferiprone*	treatment of chronic iron overload	Haematology
PERS	Risperidone	treatment of conduct disorder treatment of schizophrenia	Child & adolescent psychiatry
NEuroSIS	Budesonide*	prevention of bronchopulmonary dysplasia	Respiratory and cardiovascular disorders

* received an Orphan Drug designation (four in the same indication addressed by the project)

Ruggieri et al., Eur J Pediatr 2015

Marketed repurposed paediatric medicines

ema.europa.eu/en/news/first-paediatric-medicine-treat-rare-hormonal-disorder

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First paediatric medicine to treat rare hormonal disorder

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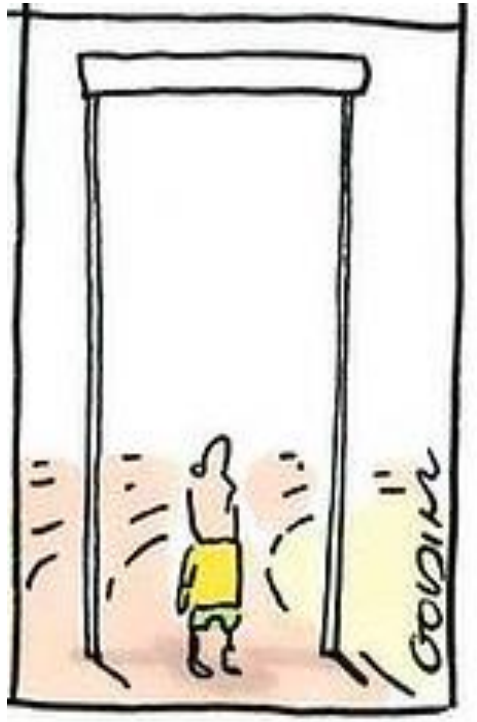
Press release 15/12/2017

CHMP gives positive opinion to Alkindi for paediatric-use marketing authorisation

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended granting a paediatric-use marketing authorisation (PUMA) for Alkindi (hydrocortisone) for the treatment of primary adrenal insufficiency, a rare hormonal disorder, in infants, children and adolescents.

Primary adrenal insufficiency is a condition where the adrenal glands (located just above the kidneys) do not produce enough of a steroid hormone called cortisol (also known as the stress hormone because it is released in response to stress). Symptoms include weight loss, muscle weakness, fatigue, low blood pressure, low blood sugar, disturbances in sodium and potassium balance and sometimes darkening of the skin. Adrenal

Which are the barriers?



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Challenges to paediatric repurposing

1. Available clinical or preclinical data may be outdated/not satisfactory to update the benefit/risk profile
2. Trials challenges: medicinal products can be used off-label anyway
3. Compliance with the relevant regulatory requirements *(even in case academic groups are in charge of developing formulation/sponsoring trials!)*
4. Price&reimbursement, access challenges

Points for discussion

- Repurposing represents an opportunity to generate evidence for paediatric medicines to cover unmet medical needs and to make paediatric drug R&D faster and easier
- Specific methods are needed to inform on the new therapeutic use
- Which solutions to overcome the barriers?

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