PROPHARMA GROUP®

Complex Challenges. Exceptional Solutions.

Paediatrics and medicines

European regulations

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Regulatory Affairs

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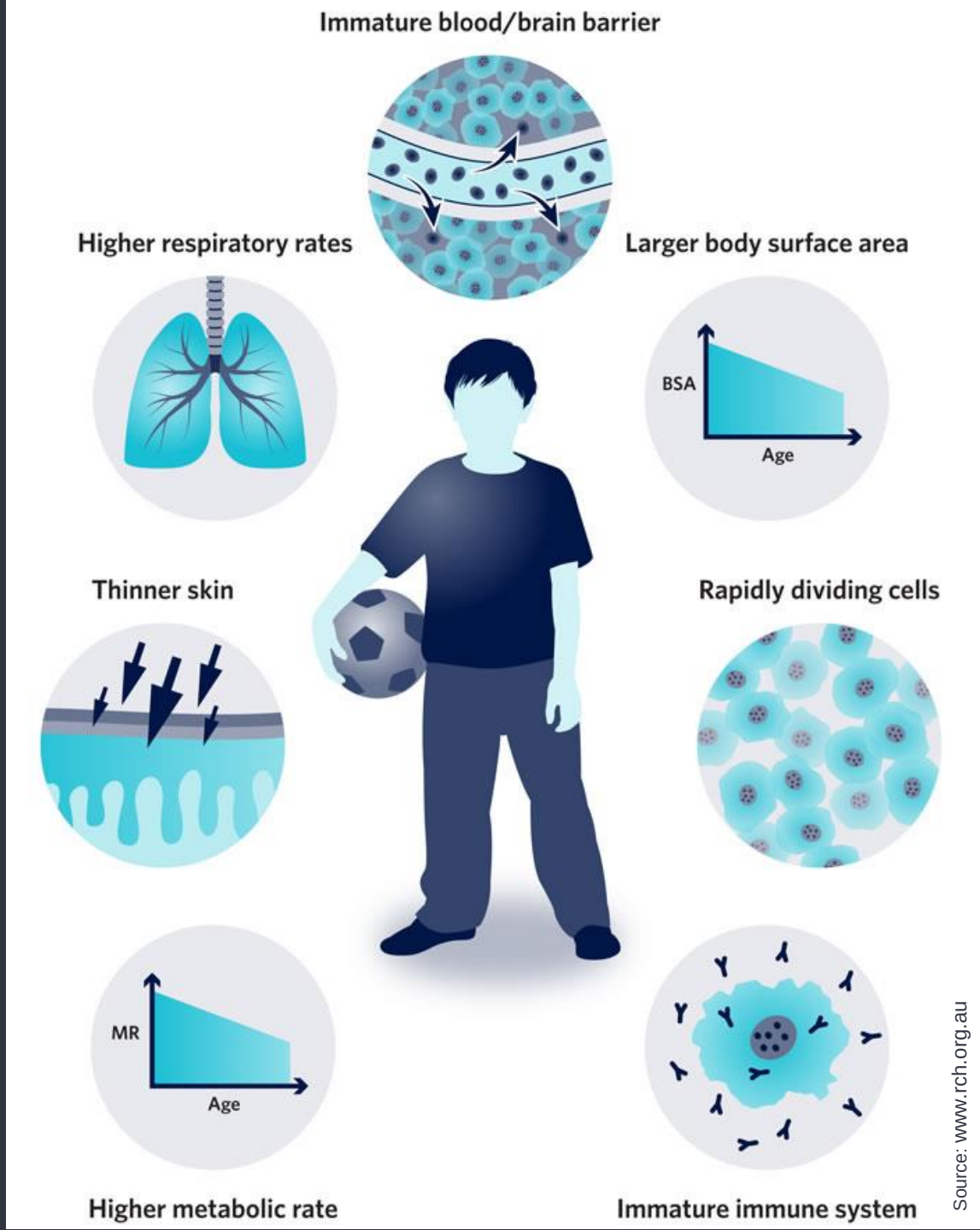
Heterogene population

Differences in PK and PD

- absorption
- distribution
- metabolism
- elimination

child ≠ little adult



Evidence of harm from off-label or unlicensed medicines in children

Report by EMA in 2004 – prior to paediatric legislation

- 820 suspected serious ADRs reported (Eudravigilance) in paediatrics receiving product* in a for EU unlabeled use
  - 130 reported as fatal
  - 361 reported as (prolonged hospitalization)
- Adverse events:
  - Neuro-psychiatric ADRs: 26% paediatrics vs 14% adults of all reports

→ Numbers are likely higher as there is generally underreporting of ADRs particularly if product unlicensed or off-label

* Registered throuh centralized procedure

Need for paediatric regulation

- Widespread off-label use in children
- Limited clinical study data in children
- Lack of appropriate pharmaceutical formulation to administer in children → unwanted side effects or under-dosing without expected efficacy

→ Need for legal obligation for pharmaceutical companies to stimulate pediatric development to become integral part of drug development

Objective paediatric regulation
Regulation 1902/2006 – effective January 2007

- Improving medicines for children:
  - Facilitating development & availability for children
  - Ensure high quality medicines for children
  - Ensure ethical research into medicines for children
  - Improve availability of information on the use of medicines for children
- Ensure development of age appropriate pharmaceutical form
- Decrease off label use

No unnecessary studies in children without delaying authorization in adults

What is a PIP (1/2)
Paediatric Investigation Plan

Research and development program aimed at generating data for a pediatric indication ➔ document defining the base for development & authorization of medicinal product for the pediatric population

- Evaluate drug in paediatric population from birth <18yrs
  - Age subsets: neonates, 0<28days, 28days<2yrs, 2<12 yrs, 12<18 yrs (17yrs in US)
- Detailed plan specifies:
  - Timing & measures to demonstrate quality, safety & efficacy in all subsets of the population

What is a PIP (2/2)
Paediatric Investigation Plan

- PIP be agreed upon with Paediatric Committee (PDCO)
- Once agreed it's legally binding
  - Deferral; delay start or completion of paediatric study/studies
    - Justified on scientific, technical or public health ground
  - Waiver; exempt from paediatric development
    - Product likely ineffective/unsafe in (part of) population
    - No sgnificant benefit over existing products
    - Disease only in adults
- Possibility to apply for modifications to PIP
  - Change of timing or measure(s)
  - Change should be fully justified

When to submit a PIP

- **Article 7**: for a new MA for a medicinal product which is not authorised in the EU.
- **Article 8**: for a new indication or pharmaceutical form/route of administration for an authorised product protected by a Supplementary Protection Certificate (SPC) or a patent which qualifies for a SPC.

To have a valid marketing authorization application: Obligation to generate paediatric data according to an agreed PIP or a decision of the EMEA granting a deferral or waiver

Scope of Products

Within scope: orphan products, informed consent application, fixed-combination products, ATMPs

Outside scope: generics, hybrids, biosimilars, well-established use, homeopathic and traditional herbal medicincal products

PUMA (Paediatric use marketing authorization): off patent product, covering exclusively paediatric indication

Content of a PIP
Scientific documentation – parts B to E

Part A	**Application form** – product information, administrative and regulatory information
Part B	**Overall development** of the medicinal product (incl info on conditions)
Part C	Application for product specific **waivers**
Part D	• D1: Existing data and overall strategy proposed or the paediatric development • D2: Quality • D3: Non-clinical aspects • D4: Clinical aspects • D5: Timing of measures in the PIP
Part E	Application for **deferrals**
Part F	Annexes
Key binding element form	**Key binding elements** (main features) of measures/studies proposed to be included in PIP opinion

PIP process

- Agree on PIP through Paediatric Committee (PDCO)
  - 1 to 1.5 yrs
- Need to comply to agreed PIP
  - Carrot/stick approach
- Option to amend agreed PIP
- Following completion of paediatric development program in line with PIP → results reflected in SmPC
  - CHMP, involving PDCO and PRAC

Limitation paediatric trials

- Number of subjects
- Duration of trials
- Exclusion high-risk population
- Limited power to detect rare (serious) events

→ Need for real world evidence

Risk Management Plan (1/3)

1. Important identified risk
   - Growth retardation in children and adolescents (*corticosteroids*)
2. Important potential risk
   - Malignant neoplasm ≥ 12 years of age
   - Malignant neoplasm 6<12 yrs of age

   } *IgE*
3. Missing information
   - Off-label use
   - Use in children
   - Safety in children (*for product approved in peds*)
   - Long term safety data in children

Risk Management Plan (2/3)
Pharmacovigilance plan

- Pharmacovigilance plan
  - Targeted follow up (e.g. on malignant neoplasm)
  - Post Authorization Safety Study (PASS)
    - Understanding long term effect in paediatrics
  - Routine case reporting*
    - Age, weight, height/length, development parameters
    - Formulation, strength
    - Dosage prescribed/administered, exposure, treatment compliance
    - (Intended) indication

*GVP: Product- or Population-Specific Considerations IV: Paediatric population Population (EMA/572054/201)

Risk Management plan (3/3)
Risk Minimisation Measures

- Risk minimisation activities
  - Prevention of possible medication errors of medicinal products in the paediatric population
    - E.g. spoon
  - Additional risk minimization measure
    - Educational material for adolescents 13<18 years
      - E.g. Aripiprazol

Paediatric data collection througout LCM