SafePedrug,
the next step in ethical pediatric drug research
Prof. dr. J. Vande Walle Dr. P. De Bruyne
Paediatric drug development:
an opportunity for academia to close the gap

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September 14, 2016
• Why
• Opportunities Safepedrug: project
• Pediatric expertise center phase I-II + III-IV Studies
• Symbiosis with DRUG
• Advisory function
  – Ethical standards
  – Authorities
  – Industry
Why?
Off-label and/or unlicensed prescriptions

- 50% in general paediatrics

- 90% of prescriptions in (neonatal) intensive care
Metabolic capacity

Integumentary development

Distribution sites

Renal function

Gastrointestinal function

differences

• Size / normalization
• Growing + maturating children
  – Growth / Bone
  – Neurocognitive function
  – Sexual /puberty : sex differences
• + primary comorbidities
• Heriditary diseases : pharmacogenetica
• Rare disease
• different “pediatric” pathogenesis
• Technical (sampling volumes)
• Need for pediatric formulations
Children are not small Adults

- But have the same right on appropriate and qualitative studied drugs
- Is it ethical
- To expose children to study protocols
- To expose children to unstudied drugs
• IWT SBO PROJECT WITH A PRIMARY SOCIAL FINALITY

• Integrating multidisciplinary translational bottom-up approaches
• towards a new paradigm for paediatric investigations:
• the next step in ethical paediatric drug research
Participating partners

- **GHENT UNIVERSITY HOSPITAL**
  - *Child Hospital Princess Elisabeth, Ghent University Hospital*
  - *Bimetra*

- **GHENT UNIVERSITY**
  - *Faculty of Medicine and Health Sciences*
    - Department of Pediatrics and Genetic Medicine
    - Heymans Institute of Pharmacology
  - *Faculty of Veterinary Medicine*
  - *Faculty of Pharmaceutical Sciences*
  - *Faculty of Arts and Philosophy*

- **KU LEUVEN**
  - *Faculty of Medicine*

- **VRIJE UNIVERSITEIT BRUSSEL**
  - *Faculty of Medicine and Pharmaceutical sciences*
Rationale and aim of the project

- Identify the specific needs in paediatrics
- Demonstrate that alternative clinical study design, tailored to the diseased child is mandatory and feasible
- That integrating available PD /PK data with modelling + paediatric animal models could allow us to optimize PIP and advance paediatric studies in time
SAFE-PEDRUG workflow

WP 1: identification of needs (literature and retrospective study)

WP 2: clinical trials, the importance of surrogate parameters

WP 3: juvenile animal model

WP 4: Paediatric physiology-based pharmacokinetic (PBPK) modelling

WP 7: guidelines

WP 9: management and coordination

WP 5: critically ill children

WP 6: neonates

WP 8: ethical and legal aspects
WP3: pig as juvenile animal model

Table. Similarities between swine and human beings (from Sachs, 1994).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Human</th>
<th>Swine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (l min(^{-1}) m(^{-2}))</td>
<td>2.5-3.5</td>
<td>2.0-2.5</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>0-8</td>
<td>1-9</td>
</tr>
<tr>
<td>Right ventricular pressure (mmHg)</td>
<td>15-30</td>
<td>24-30</td>
</tr>
<tr>
<td>Pulmonary arterial pressure (mmHg)</td>
<td>15-30</td>
<td>11-24</td>
</tr>
<tr>
<td>Left ventricular pressure (mmHg)</td>
<td>100-140</td>
<td>116</td>
</tr>
<tr>
<td>Aortic pressure (mmHg)</td>
<td>70-105</td>
<td>114-126</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal concentration (mOsm l(^{-1}))</td>
<td>1160</td>
<td>1080</td>
</tr>
<tr>
<td>Maximal urine/plasma osmol. ratio</td>
<td>4.0</td>
<td>3.3</td>
</tr>
<tr>
<td>GFR (ml min(^{-1}) per 70 kg)</td>
<td>130</td>
<td>126-175</td>
</tr>
<tr>
<td>Total renal blood flow (ml min(^{-1}) g(^{-1}))</td>
<td>4</td>
<td>3.0-4.4</td>
</tr>
</tbody>
</table>

Table. Similarities between swine and human beings.

<table>
<thead>
<tr>
<th>Human</th>
<th>Swine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1 month</td>
<td>1-2 days (1.2-1.4 kg BW), neonate</td>
</tr>
<tr>
<td>2 to 12 months</td>
<td>4-5 weeks (8-10 kg BW), post-weaning</td>
</tr>
<tr>
<td>1 to 6 years</td>
<td>8-9 weeks (15-20 kg BW), full metabolic capacity and mature nephrons</td>
</tr>
<tr>
<td>6 years to puberty</td>
<td>6 months (80-90 kg BW), puberty</td>
</tr>
</tbody>
</table>
Concepts: PBPK Modelling and Simulation (M&S) in virtual populations

Johnson et al., 2010 (PedAn) Resurgence in the use of PBPK
Work package 5

WP 9: management and coordination

WP 1: identification of needs (literature and retrospective study)

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WP 8: ethical and legal aspects
Fase 0
Animal model
werking
Toxisch
carinogen Teratogeen

Healthy volunteers

Adult patients

Fase I
Fase II
Fase III
Fase IV

PIP I

Pediatric studies
As required by EMA and FDA

PK/PD pediatric population without comorbidity and "adult indication"

6 Month follow up

Expiry of patent
SAFE-PEDRUG Paradigm
SAFE-PEDRUG Paradigm

Kick-off 26 sept 2013
Aiming for “accreditation” on international standards

Phase I-II-studies

Phase III-IV-studies

Academic / investigator initiated studies

One pediatric expertise centre to perform all drug / vaccination studies according to GCP and “high accreditation levels” rather than every subdiscipline try to do it by his own
Symbiosis with D.R.U.G

- accreditation only possible with D.R.U.G.
- Pediatric part
  - Acceptance of studies
  - Feasibility
  - Portfolio of all available facilities
  - Pediatric expertise
  - Pediatric hospitalisation facilities
- D.R.U.G. = waranty for quality and quantity.
  - Accreditation
  - Study-expertise
  - Ethical standards, GCP trained nurses, CRA’s etc..
  - Logistic “pool”
Expertise

- Phd Pediatric pharmacologist: P. Debruyne
- Oncology, nephrology, reumatology, gastroenterology, pneumology, cardiology
- Designing studies
- Safety-and PIP boards:
  - Renal excretion : J. Vande Walle
  - GI reabsorption, livermetabilisation : M.Van Winckel, P. Debruyne
  - Cardiology : arrhytmias: Hans
  - Etc..
- Phd Pediatric pharmacologist: P. Debruyne
- Oncology, nephrology, reumatology, gastroenterology, pneumology, cardiology
- Designing studies, long term safety-data
- PIP and Safety boards:
  - Renal excretion: J. Vande Walle
  - GI reabsorption, livermetabilisation: M. Van Winckel, P. Debruyne
  - Cardiology: arrhytmias: Hans Dewilde
  - Orphan diseases
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