MEDICINES FOR CHILDREN
the paediatricians perspective

José Ramet MD PhD
National Medical Associations (and, where relevant, craft, specialist scientific organisations) in the EU, EFTA and in certain cases other European countries, Hungary, Malta, Cyprus, Slovenia, etc.
Introduction

Treated with a medicine

ADULT
- sure: extensively tested
- to assure
  - safe
  - effective
  - high quality for use

CHILD
- may not be true
- over 50% of those used particularly in specialized medicine
- Potential risk
  - lack of efficacy
  - unexpected adverse effects
  - even death
Historical background

- Drug catastrophes involving mainly children
  - sulphanilamide 1937
  - thalidomide 1962

- Development of regulations concerning medicinal products

- Stringent criteria of (pharmaceutical)
  - Quality
  - Safety
  - Efficacy

Unfortunate paradox: children benefited the least

“Therapeutic orphans”

H. Shirkey 1963: reflect problems re. regulatory requirements
Current situation

- European Union
  - 0-16 years : about 75 million people

- 0-16 years group : specific sub-populations
  - Age groups: different developmental and behavioural characteristics
  - Age-specific needs
## European pediatric hospitals

<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>Unit</th>
<th>Off-label</th>
<th>Unlicensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conroy</td>
<td>1998</td>
<td>Gen ped Hosp</td>
<td>39%</td>
<td>7%</td>
</tr>
<tr>
<td>Turner</td>
<td>1996</td>
<td>PICU</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td>Conroy</td>
<td>1999</td>
<td>NICU</td>
<td>55%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Consequences of unlicensed and off-label use of medicines in children

- Quality
- Safety
- Efficacy
Analgesia
Sedation
Antibiotics
Paralyzing drugs
Gastric protection
...
...
Consequences of unlicensed and off-label use of medicines in children

- **Quality:**
  - absorption characteristics and bioavailability unknown
  - most likely risk:
    - inaccurate dosing
    - inefficiency

- **Safety:** unknown adverse effects

- **Efficacy:**
  - new major therapeutic breakthroughs: not available for children
    - treated with older - less efficacious - products
    - new medicines used without appropriate studies
      - not same efficacy as in adults / effect not similar
      - increase morbidity and mortality of children
Indications... without research

- Promising case report published
- Uncontrolled study suggests benefit
- Use: standard for many years
Empiricism

- Empiricism: wrong?

- No, but
  
  Difficult to accept
  
  If strong evidence missing: rely on ... absence of data

  - Uncontrolled studies
  - Case reports / anecdotical reports
  - Not published information
  - Meta-analysis
    - Negative studies not published
    - Homogeneity bias
    - Size
    - Blinding
Child... Not a small adult
Infant... Not a small child
Preterm... Not a small infant

- Studies in adults not sufficient
  - Specificity disease
  - Kinetic characteristics
  - Effects on growth, development, maturation
  - Specific adverse reactions

- Additional problems
  - Incapable give legal consent
  - Medicines if clinical value
  - Best possible protection
  - Minimization risk and pain
EU regulatory initiatives on pediatric medicinal products?

- 1. Increase the availability medicinal products
- 2. Ensuring that pharmacovigilance mechanisms are adapted
- 3. Avoiding unnecessary studies
- 4. Procedure for determining priorities for research
- 5. Joined European efforts
- 6. Highest ethical criteria
initiatives on paediatric medicinal products?

1. **Increase the availability** medicinal products suitably adapted to the needs of children by encouraging:
   - appropriate pediatric studies on new medicinal products
   - studies on existing products
   - development of suitably adapted formulations

2. **Ensuring that pharmacovigilance mechanisms are adapted**
   - Possible long-term effects in specific cases

3. **Avoiding unnecessary studies**
   - Publication of details of clinical trials already initiated

4. **List of priorities for research**
   - on existing medicinal products
   - in accordance with health needs
   - priorities in different therapeutic classes

5. **Expert group**
   - in the field of research
   - development and assessment of clinical trials

6. **Highest ethical criteria**
Avenues to explore

- Positive Incentives for research
  - specific rules to encourage the performance of clinical trials in children

- Legal EU requirements
- Transparency and central database
- Scientific expert group
- European network of clinical excellence
Future?

“It is difficult to make predictions
... especially about the future”

Y. Berra