Specific Challenges for Orphan Drugs with Paediatric Development

Tsveta Schyns-Liharska, PhD
ENRAH
Member of the PDCO, EMA
Representing Patients and EURORDIS
Disclaimer

Some of the slides in this presentation are based on EMA sources which are gratefully acknowledged but the opinions are to be considered personal.
The Historical Paediatric Situation

20% of the EU population, i.e. 100 million, is aged less than 16 years: premature neonate, term neonate, infant, child, adolescent

- 50-90% of paediatric medicines have not been tested and evaluated
- US paediatric data (Best Pharmaceuticals for Children Act) not submitted to EU Agencies
- Around 75% of all 317 centrally authorised MPs relevant for children and only half (34%) with a paediatric indication

- Risks:
  - adverse effects (overdosing)
  - inefficacy (under-dosing)
  - improper formulation
  - delay in access to innovative medicines
EU Regulations

• Market forces alone had proven to be insufficient incentive for adequate research, development and authorisation of medicinal products for:
  – Patients with rare disease - Regulation (EC) No 141/2000
  – Paediatric population - Regulation (EC) No 1901/2006 with Incentives and Obligations
## EU Paediatric Regulation: Obligations and Incentives

<table>
<thead>
<tr>
<th>Type of MP</th>
<th>Obligation</th>
<th>Incentive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>New MP</td>
<td>Paediatric Investigation Plan or Waiver</td>
<td>6 months extension of SPC (patent)</td>
<td>Necessary for validation of application</td>
</tr>
<tr>
<td>On Patent and authorized Medicine</td>
<td>Paediatric Investigation Plan or Waiver</td>
<td>6 months extension of SPC (patent)*</td>
<td>When new indication or new route or new pharmaceutical form: necessary for validation</td>
</tr>
<tr>
<td>Orphan Medicine</td>
<td>Paediatric Investigation Plan or Waiver</td>
<td>2 additional years of market exclusivity</td>
<td>10+2 years of market exclusivity Article 37</td>
</tr>
<tr>
<td>Off patent Medicine</td>
<td>None (voluntary PIP possible for PUMA)</td>
<td>10 years of data protection</td>
<td>Research funds Paed. Use MA (PUMA)</td>
</tr>
</tbody>
</table>

Centralised procedure * Free Scientific Advice /Protocol Assistance* Fee waived
Milestones in the development of the Paediatric regulation

- **1997**: US BPCA approved
- **December 1999**: first draft document to Council of EU Health Ministers:
  - EU Orphan regulation (1999) used as example
- **December 2000**: EU Health Ministers urge the EU Commission to draft Paediatric legislation
- **2004**: First draft prepared regulation
- **Dec 2004-Jun 2006**: Consultations and final draft
Milestones in the Paediatric Regulation

- **26 January 2007**: entry into force of the Paediatric Regulation: Free EMA “paediatric” scientific advice
- **4 July 2007** (6 months from entry into force): Paediatric Committee (PDCO) first meeting
- **26 July 2008** (18 months from entry into force): Applications for MA (new products) should contain results of studies conducted in compliance with agreed PIP (unless: waiver or deferral)
- **26 January 2009** (24 months from entry into force): Same obligation extended to applications for new indication, new route of administration or new pharmaceutical form for authorised “patented” products
Pillars of the Paediatric Regulation

• Paediatric Committee (PDCO)
• Paediatric Investigation Plan (PIP)
• A system of obligations and rewards
• Transparency measures
• Other measures
The Paediatric Committee
PDCO. 1

- >60 members/alternates nominated from
  - within the CHMP
  - the Member States
  - healthcare professionals' organisations
  - patient organisations
  (not EMA staff, 3 years renewable appointments)

- First meeting: July 2007; 13-12 meetings/year
- Scientific discussions and opinions
- Expert Working groups Non clinical and Formulations
PDCO.2

- **Involves** external experts on scientific questions raised by paediatric development to improve the PIPs
- **Consults** patient representatives and patient organisations on issues concerning trail design
- **Communicates** with FDA and internally with the EMA Scientific Committees
PDCO. 3

• Provides expertise to EMA Scientific Advice / Protocol Assistance procedures addressing paediatric questions
  – 70 per year
  – over 150 companies benefited from Scientific Advice on paediatric questions, provided by either Member States directly or the EMA/CHMP

• Decides on the PIPs
Paediatric Investigation Plan (PIP)

• “a research and development program aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population”
  - age appropriate formulation(s)
  - Demonstrate the drug safety through animal testing
  - Demonstrate that the product is efficacious (and safe) in the relevant age-group(s)
• **Waver** if the disease does not occur or the product appears unsafe in the paediatric population

• **Defer** some studies until after the related marketing authorisation application (e.g. in adults)
  – applicant must still commit to doing the studies
  – applicant must provide detailed plans (including timelines)
  – reward will not be given until deferred studies are complete
  – PDCO may refuse a request for a deferral because the data are needed as soon as possible
Role of the PDCO in the regulatory Process

COMP(Optional request)

CHMP

Scientific Advice/Protocol Assistance

Clinical development

Non-clinical  I  II  III

PIPlan (Waver)  Modifications  Compliance

Approval

Post-approval

MA

PDCO

the number of modifications of agreed PIPs per year is ~ ½ of newly agreed PIPs for that year
1000th application to the PDCO October 2010

• ~15% of the application are for products with orphan designation

• 682 PDCO Decisions on PIP applications:
  – 476 agreed PIPs (70%) (30% wavers: not applicable to the paediatric population or unsafe)
    • 75% of PIPs concern new/not yet authorised medicines/article 7 PR
    • 7 PIPs out of PUMA (20 off-patent medicines for paediatric use in 15 projects funded by the EU FP)
Orphan Designations for the treatment of conditions that affect exclusively children, or both adults and children, has increased ~30% of orphan designations affect only children and in some of these no alternative treatments exist.
Orphan Products addressing unmet paediatric therapeutic needs

- 17 designations adapting the pharmaceutical form to the needs of paediatric age groups
- 2 MA of OPs with pharmaceutical forms that address specific needs of the paediatric population
- no orphan-designated product has yet obtained the orphan incentive of two additional years of market exclusivity (after completing paediatric studies in compliance with an agreed PIP) (Article 37)
Orphan Drug Development in the Paediatric Population

Major hurdles and concerns:
• low numbers
• expertise and clinical centres
• natural history

➢ feasibility of clinical trials
Predictable Flexibility

- Flexible criteria for a rare disease on
  - Endpoints
  - Study population size
  - Design
• Extrapolation of efficacy from adults to avoid unnecessary studies in children (22 % of PIPs)

• The condition is rare in the EU but prevalence is high in countries outside EU :
  • clinical studies are conducted exclusively in the relevant countries following the Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities (16th April 2012)
New approaches: Study design

• For a very rare condition several PIP’s are submitted for MP that are bio-similar:
  – a limited number of patients in phase III clinical studies (30)

However: concerns remain about the feasibility of all the necessary studies and comparability of data to address unmet needs in the paediatric population

– Designing a multi-product, multi-company study?
New approaches: Study design

• Ultra rare condition (50 cases in a year in several centres) and good knowledge of natural history of the disease:
  – Pivotal study: single arm, non-randomized, open label, multi-site, single dose study with 15 patients. Plus, a retrospective studies on natural history of the disease –end points

• Use of Validated Surrogate Endpoints
Specific Challenges for Orphan Drugs with Paediatric Development

Thank you!