Regulatory incentives: Experience from European Medicines Agency

European Medicines Agency

Presented by: Nathalie Seigneuret
EU Paediatric Regulation: Objectives

• Improve the health of children:
  – Increase high quality, ethical research into medicines for children
  – Increase availability of authorised medicines for children
  – Increase information on medicines

• Achieve the above:
  – Without unnecessary studies in children
  – Without delaying authorisation for adults
Pillars of the Paediatric Regulation

- Paediatric Committee
- Paediatric Investigation Plan
- A system of OBLIGATIONS and REWARDS
- TRANSPARENCY MEASURES
- OTHER MEASURES
Paediatric Committee (PDCO)

CHMP: Committee for Human Medicinal Products

- CHMP members (5)
- Patient/family and health-care professionals (6)
- Experts from National Competent Authorities (22) + EEA
- + alternates

1 Chair elected
Paediatric Committee (PDCO)

- Wide range of specialities represented (e.g. neonatology, paediatric cardiology, immunology, transplantation, respiratory, oncology..)

- Formulation Working Group

- Non-clinical Working Group

- Extrapolation Working Group

- Interaction with experts, learned societies as needed
Paediatric Investigation Plans

Details of timing and measures proposed necessary to obtain a paediatric indication with an age appropriate formulation in all paediatric subsets affected by the condition i.e non-clinical, clinical studies, trials & pharmaceutical development

- Quality
- Safety
- Efficacy

Marketing Authorisation criteria
Waivers:

Three types:

- **“total” (product-specific) waiver** → for all conditions/indications being applied for a product
- **partial waiver**: one and more subset(s), indication(s), but there is a PIP!
- **Class waiver**: for a class of products in a condition, or for all products aimed at a condition – List adopted by the PDCO

Legal grounds:

- Lack of efficacy and safety
- Disease or condition occurring only in adults population
- Lack of significant therapeutic benefit
Deferral(s):

Instrument to ensure that the research is conducted only when safe and ethical.

“Deferred” means Marketing Authorisation Application for adults is possible before initiation/completion of one or more measures in the PIP.
EU Paediatric Regulation: Obligations

1) Currently unauthorised medicinal products

Results of agreed PIP at time of marketing authorisation application, OR waiver/deferral

2) Authorised patented medicinal products

Results of agreed PIP at time of application for new indication, new route of administration, new formulation, OR waiver/deferral

3) Orphan medicinal products

Same obligations

4) Off patent medicinal products: Paediatric Use Marketing Authorisation (PUMA)

- Optional: covers Paediatric Indication and Formulation
Rewards

Reward is given for all PIPs correctly completed, but PIPs are “always” required

- if development is compliant with agreed PIP (compliance statement in MA);
- if results of studies included in Summary of PC + patient’s leaflet;
- if product is authorised in all MSs (except for PUMA):
  - Non-orphan products: 6-month extension of SPC (patent protection)
  - Orphan medicinal products: + 2 additional years of market exclusivity
  - PUMA: 8+2 years of data+market protection

- Product-specific or class waiver does NOT trigger the reward
- «negative» PIP results do allow reward
- Inconclusive studies in PIP do NOT trigger the reward
Opinions and Decisions on Paediatric Investigation Plans (PIPs)

This search allows you to find information on opinions and decisions on a Paediatric Investigation Plan (PIP) including deferrals and waivers. A PIP is a development plan aimed at ensuring that the necessary data is obtained through studies in children to support the authorisation of the medicine for children. The plan is submitted by a pharmaceutical company to the Paediatric Committee (PDCO) at the European Medicines Agency which is responsible for agreement or refusal of the plan and publishes an opinion with its decision.

Decision types
P: decision granting a waiver in all age groups for all conditions/indications
PM: decision on the application for modification of an agreed PIP
RW: decision refers to a refusal on a proposed Paediatric Investigation Plan
WW: decision refers to a refusal on a request for request on a waiver in all age groups

Browse the database based on therapeutic area:
- Infectious diseases

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Decision Type</th>
<th>Therapeutic area</th>
<th>PIP number</th>
<th>Decision date</th>
<th>Last updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2S,3S,8R,10R,11S,12R,14R)-(cyclopentylsulfonfyl)-2-[2-(4-isopropyl-1,3-thiazol-2-y1)-methoxy-5-methyl-4-quinolinyl(oxyl)-3-methyl-4,11-diazocyclo-2,3,8,4,6,7,9,11b,12,13,14,16,18-triene-1-carboxamide]</td>
<td>P</td>
<td>Infectious diseases</td>
<td>EMA-000025-PIP01-09</td>
<td>07/04/2010</td>
<td>18/05/2010</td>
</tr>
<tr>
<td>Adderin, hydrocortisone</td>
<td>W</td>
<td>Infectious diseases</td>
<td>EMA-000110-PIP01-07</td>
<td>15/08/2008</td>
<td>18/09/2008</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>P</td>
<td>Infectious diseases</td>
<td>EMA-000049-PIP01-08</td>
<td>31/03/2010</td>
<td>18/05/2010</td>
</tr>
</tbody>
</table>
A. CONDITION(S)
Human Immunodeficiency Virus (HIV-1) infection

B. WAIVER
Not applicable.

C. PAEDIATRIC INVESTIGATION PLAN
• Condition to be investigated
Human Immunodeficiency Virus (HIV-1) infection in ARV-naïve patients
• Proposed PIP indication
Rilpivirine is indicated in combination with other antiretroviral (ARV) medicinal products, for the treatment of human immunodeficiency virus (HIV-1) infection in ARV-naïve paediatric patients of all ages.
• Subset(s) of the paediatric population concerned by the paediatric development
From birth to less than 18 years.
• Formulation(s)
- Tablets for oral use
- Age-appropriate formulation under development (granules or oral solution or oral suspension) for oral use

Example of public information on Decision: rilpivirine 1/2
Example of public information on Decision: rilpivirine 2/2

Studies:
Quality: Age-appropriate formulation for oral use
Clinical
1- Open-label, randomized, crossover trial to compare the oral bioavailability of the age-appropriate pediatric formulation(s) of Rilpivirine hydrochloride.
2- Multi-center, open-label, noncomparative study in HIV-1 infected treatment-naïve adolescents from 12 years to less than 18 years.
3 - Multi-center, open-label, noncomparative study in HIV-1 infected treatment-naïve children from birth to less than 12 years of age

Measures to address long term follow-up of potential safety issues in relation to paediatric use: Yes

Date of completion of the paediatric investigation plan: By December 2015

Deferral for some or all studies contained in the paediatric investigation plan: Yes
# Number of Applications

<table>
<thead>
<tr>
<th>Category</th>
<th>2008 (January to December)</th>
<th>2009 (January to December)</th>
<th>2010 (January to current month)</th>
<th>Cumulative total (2007 to 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of validated PIP/waiver applications</td>
<td>271</td>
<td>273</td>
<td>277</td>
<td>907 [1]</td>
</tr>
<tr>
<td>Applications submitted for a product not yet authorised (<em>Article 7</em> [2])</td>
<td>186</td>
<td>191</td>
<td>239</td>
<td>655 (72%)</td>
</tr>
<tr>
<td>Applications submitted for a product already authorised and still under patent, in view of a submission of a variation/extension for a new indication, pharmaceutical form or route of administration (<em>Article 8</em> [2])</td>
<td>75</td>
<td>72</td>
<td>37</td>
<td>229 (25%)</td>
</tr>
<tr>
<td>Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation (<em>Article 30</em> [2])</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>23 (3%)</td>
</tr>
<tr>
<td>PIPs and full waiver indications covered by these applications</td>
<td>395</td>
<td>395</td>
<td>322</td>
<td>1283</td>
</tr>
</tbody>
</table>

[1] Of which 198 have been requests for a full waiver.
## PDCO opinions

<table>
<thead>
<tr>
<th>Number of Paediatric Committee (PDCO) opinions</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>Cumulative total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on full waiver</td>
<td>48</td>
<td>67</td>
<td>37</td>
<td>161</td>
</tr>
<tr>
<td>Positive on PIP, including potential deferral</td>
<td>81</td>
<td>122</td>
<td>64</td>
<td>269</td>
</tr>
<tr>
<td>Negative opinions adopted</td>
<td>4</td>
<td>13</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Positive opinions adopted on modification of a PIP</td>
<td>8</td>
<td>51</td>
<td>69</td>
<td>128</td>
</tr>
<tr>
<td>Negative opinions adopted on modification of a PIP</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Positive opinions on compliance with a PIP</td>
<td>5</td>
<td>8</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Negative opinions on compliance check with a PIP</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
As of December 2009....

- Completion of PIP and opinion on compliance:
  6 products (caspofungin, ribavirin, peginterferon alfa-2b, valsartan, anastrazol, losartan)

  Already extension of patent in some EU MS

- Record of waiver and deferral included in product information of 10 medicinal products (e.g. abatacept)

- So far no companies have benefited from 2-year extension of market exclusivity for an orphan medicinal product, nor from the data and marketing protection periods granted for PUMA.
Provision of Information

Paediatric clinical trials in EUDRACT:

- To include protocols and results of all clinical trials
- To include third countries trials linked to a PIP
- Paediatric information to be made public
- Currently the number of clinical trials involving children has not increased (10% of trials)

Public access to paediatric information for authorised products (EudraPharm)
“Articles 45 and 46”

- Art. 45: all **existing** paediatric studies to be submitted →
  ~ 80 centrally approved products
  ~ 1000 nationally approved active substances

- Art. 46: results of all **new** paediatric studies, **sponsored by applicant**, to be submitted to EMEA/NCA within 6 months of completion (Last Patient Last Visit), whether part of a PIP or not.

- Few modifications of Product information e.g change in dose recommendations for amlodipine and simvastatine - telithromycin
Off-label use of medicinal products in children:

- Aim: to identify the needs in the different therapeutic areas where there should be research and development of medicinal products, either old (i.e. off patent) or new ones.
- Consultation of EU member states, learned societies.

- Survey of use of existing medicines: results currently analysed
# List of Paediatric Needs (e.g. nephrology)

<table>
<thead>
<tr>
<th>LOOP DIURETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUROSEMIDE</strong></td>
</tr>
<tr>
<td><strong>Authorised indication</strong>: Oedema and hypertension</td>
</tr>
<tr>
<td><strong>Authorised age group</strong>: All age groups <em>(France)</em></td>
</tr>
<tr>
<td><strong>Authorised dose</strong>: 400–600 μg/kg/day in all age groups <em>(Finland)</em></td>
</tr>
<tr>
<td><strong>Authorised formulation</strong>: Solution for injection, Tablets, Oral solution</td>
</tr>
<tr>
<td><strong>Needs</strong>: Data on PK, efficacy and safety in indications renal failure and renal hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>BUMETAMIDE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authorised indication</strong>: Oedema</td>
</tr>
<tr>
<td><strong>Authorised age group</strong>: &gt; 12 years <em>(United Kingdom)</em></td>
</tr>
<tr>
<td><strong>Authorised dose</strong>: 1-2 mg (i.v. injection)</td>
</tr>
<tr>
<td><strong>Authorised formulation</strong>: Tablets, solution for injection</td>
</tr>
<tr>
<td><strong>Needs</strong>: Data on PK, safety and efficacy in children &lt; 12 years</td>
</tr>
</tbody>
</table>
Priority List of off-patent medicinal products

- Funding of studies for off-patent medicinal products provided by Paediatric Regulation through the EU Framework Program 7 (FP7)
- List of priorities revised annually by EMA. Shared with FDA/NIH to avoid overlap or duplication of efforts, and facilitate multinational trials where necessary
- The list is adopted after public consultation and is not ranked
- Used by EU Commission to assign FP7 funds to projects
- July 2010 publication revised list for the 5th call 2011
Priority List of off-patent medicinal products

2008
1) Development of oral liquid formulations of Methotrexate and 6-Mercaptopurine for paediatric acute lymphoblastic leukaemia
2) Evaluation PK & PD of ciprofloxacin and fluconazole in neonates.
3) Oral liquid formulations of Cyclophosphamide and Temozolomide.
4) Efficacy of Budesonide in reducing bronchopulmonary dysplasia.
5) Aims to evaluate pharmacokinetics and pharmacodynamics of doxorubicin.
6) Comparison morphine and fentanyl in pain relief in pre-term infants.

2009
1) Evaluates the efficacy safety, PK, PD, mechanisms of action of bumetanide in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns
2) European multicentre network to evaluate pharmacokinetics, safety and efficacy of Meropenem in neonatal sepsis and meningitis.
3) Use of risperidone in children and adolescents with conduct disorder who are not mentally retarded, and the use of risperidone in adolescents with schizophrenia.
European Paediatric Research Network

**ENPREEMA**: To link together existing networks, investigators and centres with specific paediatric expertise. Build up competences at a European level.

**Facilitate the conduct of studies**

**Avoid duplication of studies**

- Strategy published
- Networks and centres identified (50+) and invited (2009 & 2010)
- 2 working groups:
  - One on organisation and functioning
  - One on criteria (‘recognition’)
- Both have completed the work and self-assessment by existing networks in progress
Collaborations

• FDA: paediatric cluster with FDA
• Health Canada Japan (confidentiality Agreement)
• WHO ("Making Medicines Child Size", 2008; Network of Regulatory Agencies on Paediatric Medicines)
• ICH → guidelines on paediatrics:
  - Paediatric formulations
  - ICH E11
  - Juvenile animal studies?
  - PK for modelling, etc.
(not on the agenda for the time being)
• EU Commission
Conclusions

• Impact on workload and resources
• Most legal deadlines have been met with success
• Real awareness of need of good development of medicines in children
• No evidence yet of increase in clinical trials
• Positive collaboration within and outside the Agency
• Product information changes already visible
• Annual report on benefits/infringement to Regulation published
Thank You