AGAH

Workshop

PAEDIATRIC INVESTIGATION PLAN
How to Adapt Clinical Development to the Particularities of Paediatrics?

13. – 14. 01. 2009
Bonn

Birka Lehmann
• EMEA’s/PDCO’s expectations and experiences with submitted PIPs,

• Regulatory requirements for PIPs with
  • new drugs,
  • marketed and
  • out-of-patent drugs

• New paediatric formulations
PIP and Consequences

- Clinical trials application: Ethics Committees & national competent authority
- Validation of MA application – COMPLIANCE CHECK
- MA with SmPC & PL

*Ethics Committee & **national competent authority
### D.1.2 Selected age group(s)

...should cover all subsets of the paediatric population, including neonates, which are not covered by a waiver.

### D.4: Strategy in relation to clinical aspects (PIP indications and age subsets)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Safety</th>
<th>Dose/dosage</th>
<th>Age appropriate formulation</th>
</tr>
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<tbody>
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</table>

#### A.1.5. Selected age group(s)

**Pre-term Infant**
- < 36 weeks gestation

**Term Newborn**
- 0–27 days

**Infant/Toddler**
- 28 days

**Child**
- 2 – 11 years

**Adolescent**
- 12 – end of 17 years

Survival: Adaptation, Growth, Training, Maturation
• EMEA’s/PDCO’s expectations and experiences with submitted PIPs,

• Regulatory requirements for PIPs with
  • new drugs,
  • marketed and
  • out-of-patent drugs

• New paediatric formulations
Reg. 1901/2006
12 December 2006

Art 2(2) Paediatric investigation plan indication – condition

New: CommComm PIP
24 September 2008

,Condition‘
,Paediatric investigation plan indication‘
,proposed therapeutic indication‘

Condition – vs – definition of waiver request

The specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population

The disease or condition for which the specific medicinal product or class is intended occurs only in adult populations

The specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients
Based on the provisions set out in Article 11–13 of the Paediatric Regulation, the PDCO proposes to grant a class waiver for the following indications (condition) publication 21 April 2008
Reg. 1901/2006  
12 December 2006

Art 2(2) Paediatric investigation plan indication – condition

New: CommComm PIP  
24 September 2008

'Condition'

'Paediatric investigation plan indication'

'proposed therapeutic indication'

Condition – vs – definition of waiver request

Content of PDCO opinion/EMEA decision

Information in cover letter
• EMEA’s/PDCO’s expectations and experiences with submitted PIPs,

• Regulatory requirements for PIPs with
  • new drugs,
  • marketed and
  • out-of-patent drugs

• New paediatric formulations
Application for marketing authorisation for medicinal products

- Article 7
  26.07.2008 = application of new medicinal products with PIP and results of studies according to PIP

- Article 8
  26.01.2009 = Line-Extensions (with Supplementary Protection Certificate/Patent)

- Article 30
  Paediatric Use Marketing Authorisation (PUMA) – off patent medicinal products
New: Communication from the Commission
The Paediatric Investigation Plan (PIP)
24 September 2008

SECTION 1 – FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS OR DEFERRALS

2.1 – GENERAL PRINCIPLES AND FORMAT

The same application form (see the Annex to this guideline) should be used whether requesting agreement to a paediatric investigation plan, a waiver, a deferral or a combination thereof. Different parts (Part A to Part F) of the application are provided to fulfil the different types of request.

Part C: Application for product specific waivers

Part E: Application for deferrals
New: The Paediatric Investigation Plan (PIP)

D.5.4: Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies or trials

— type of study,
— study design,
— type of control (placebo or active control with dose to be used) and justification,
— location (regions),
— test(s) products; dosage regimen; route of administration,
— objective(s) of the study,
— number of subjects (M/F), ages, number per ICH age groups or other relevant age group,
— duration of treatment including the duration of post-treatment observation,
— main inclusion/exclusion criteria,
— parameters or endpoints (primary, secondary),
— sample size (more or less detailed as appropriate),
— power calculation: describe effect size expected,
— options in case of recruitment issues, interim analyses and stopping rules,
— statistical methods (Statistical methods used to compare groups for primary outcome, and for additional analyses if relevant).
Paediatric Investigation Plan (PIP)

Design of clinical trials

- Feasibility of the trial to be performed
  - Size of trial
  - Ethnic groups (genetic characteristics)
  - Blinded/un-blinded

- Use of placebo (not withholding effective treatment)
  - Comparator (unlicensed??)

- Pain, distress and fear minimisation
  - Risk assessment and monitoring
  - Benefit and measures of benefit
The Paediatric Investigation Plan (PIP)

Extrapolation: ?Efficacy – Safety?

Adult

Adolescent → Child → Infant/Toddler → Term Newborn → Pre-term Infant
Guidelines on indication/conditions

Addendum (Annex) for paediatric population

Why?

- Diagnostic

- Endpoints – measurement/monitoring

- Monitoring
Addendum for paediatric population

Why?

- **Endpoints**
  The suitability of **6-Minutes Walk Test** as a primary endpoint should be discussed considering it is influenced by age, ... and degree of motivation.
  - Other endpoints could include functional tests (e.g. cardiopulmonary exercise testing, shuttle walk test), biomarkers, or the development of a PAH-specific quality of life questionnaire.

(Possible) Recommendation

- **Endpoints? Pulmonary vascular resistance**
  Invasive (right cardiac catheterization) / non-invasive (echocardiography/Doppler) for children under (6?) years of age – correlation clinical score.
Part E: Applications deferrals

Pursuant to Article 20(1) of the paediatric regulation, a request may be made for deferral of the initiation or completion of some or all of the measures.

With reference to the timelines stated in Section D.5.1, and to which
- indication,
- route of administration
- pharmaceutical form.
- The application should specify the age group to which it applies.

For timelines, specific months and years should be given also in relation to the development in adults.

Requests for deferrals should be justified on scientific and technical grounds or on grounds related to public health and the paediatric regulation requires that a deferral be granted when:
— it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population,
— studies in the paediatric population will take longer to conduct than studies in adults.

Other examples of scientific and technical justification for a deferral may include when additional non-clinical data are considered necessary or when major quality problems currently prevent development of the relevant formulation(s).
Timelines PIP

Day 30
first discussion in PDCO

Rapporteur
20 days

Peer Reviewer
8 days

Day 60
Sec. discussion in PDCO + OE

Day 90
first disc. in PDCO after modification by applicant

Rapporteur
20 days

Peer Reviewer
8 days

Day 120
Final discussion in PDCO + OE

Day 1
Validation - EMEA Summary Report

Day 61
Update Summary Report

Adoption of Opinion or List of outstanding Issues

Adoption of opinion

OE = Oral Explanation

EMEA decision addressed to applicant

Clock stop

Re-start

60 Days

60 Days

+/- 3 months
### OVERVIEW OF PAEDIATRIC INVESTIGATION PLAN/WAIVER APPLICATIONS

<table>
<thead>
<tr>
<th></th>
<th>2007 (August to December)</th>
<th>2008 (January to December)</th>
<th>Cumulative Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of validated PIP / waiver applications</td>
<td>85</td>
<td>271¹</td>
<td>356²</td>
</tr>
<tr>
<td>Applications submitted for a product not yet authorised <em>(Article 7)</em></td>
<td>39</td>
<td>186</td>
<td>225 (63%)</td>
</tr>
<tr>
<td>Applications submitted for a product already authorised 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></td>
<td>45</td>
<td>75</td>
<td>120 (34%)</td>
</tr>
<tr>
<td>Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation <em>(Article 30)</em></td>
<td>1</td>
<td>10</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>PIPs and full waiver indications covered by these applications</td>
<td>202</td>
<td>395</td>
<td>597</td>
</tr>
</tbody>
</table>

### Number of Paediatric Committee (PDCO) opinions

<table>
<thead>
<tr>
<th>Opinions</th>
<th>2007</th>
<th>2008</th>
<th>Cumulative Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on full waiver</td>
<td>10</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Positive on PIPs including potential deferral</td>
<td>2</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>Negative opinions adopted</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Positive opinions adopted on modification of the PIP</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Positive opinion on compliance with PIP</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**CORE:** data collection and verification

- **Article 45**
  - finalised studies

  - Paediatric Worksharing
    - Chemical = 980
    - Natural Products = 8*/ 456
    - Vaccines = 192
    - Radiopharmaceutical = 72

- **Article 46**
  - submission 6 months after finalisation

* High priority
- EMEA’s/PDCO’s expectations and experiences with submitted PIPs,

- Regulatory requirements for PIPs with
  - new drugs,
  - marketed and
  - out-of-patent drugs

- New paediatric formulations
New paediatric formulations – the challenges

Dosages according to weight (1 kg – xx kg)?

Dermal: Hydration of skin?

Oral: Dosing by mixture with food?

Parenteral: i.v. – volume/needle

Formulation
- preservatives?
- colourants?
- sweetner?

Rejection: taste and/or smell
New paediatric formulations
the challenges

REFLECTION PAPER: FORMULATIONS
OF CHOICE FOR THE PAEDIATRIC
POPULATION
(EMEA/CHMP/PEG/194810/2005)

Expert working group at EMEA/PDCO

New guideline(s)?
Thank you very much for your attention