The EU PIP - a step in Pediatric Drug Development

Thomas Severin
Bonn, 13.01.2009
Agenda

- Implications for Industry
- Company Preparation
- Time of PIP Submission
- Content of the PIP
- The PIP Process and first Experience
- Global approach to Pediatric Drug Development
- Conclusions
Integration of Pediatric Drug Development

- **From**
  - Pediatric Clinical Trials in selected areas
  - Partly unlicensed & off-label use of drugs in children

- **To**
  - New and strong reg. framework for Pediatric Medicines in EU
  - Potential of Pediatric Development to be considered for every new product early in development process
  - Dialogue with the Pediatric Committee at early stage
    - Agreement on Pediatric Investigation Plan/Waiver/Deferral
Opportunities

- Contribution to address unmet medical need
- Increase of availability of properly evaluated and authorised medicines for children
  - by generating systematic safety and efficacy data
- Increase of pediatric information on medicines
- Under specific conditions obtain potential rewards
  - to cover the investments for pediatric development
- Contribution to Better Medicines for Children
Pediatric Drug Development

Medical Needs of the Pediatric Population

Regulatory requirements

Pediatric Drug Development

Challenges of Pediatric Drug Development

Public/Patient Expectations
Implications for Industry

- Integration of pediatric aspects in development process

- Assessment of Product Portfolio for pediatric use
  - Marketed Products
  - All Products from early to late Development

- Pediatric Investigation Plans or waiver requests needed
  - for MAA of all new products since July 26, 2008
  - for new indications, pharmaceutical forms, routes of administration as of Jan. 26, 2009

- Development of new pediatric formulations

- Conduct of more pediatric clinical trials
Company Preparation

- Linking internal pediatric expertise
  - Cross-functional expert network to support development teams
  - Sharing of key information and experience
    - Regular internal communication on pediatric issues
    - Available guidances (ICH, EMEA, EC, FDA)
    - Relevant legal texts (e.g. EU Ped. Reg., FDAAA)

- Benefit of external advice
  - Expert input in pediatric development plans and protocols
  - Pediatric advisory boards
  - Cooperation with pediatric clinical research networks
  - Participation in pediatric conferences and workshops
Internal Partners

- Research
- Chemical Development
- Pharmaceutical Development
- Exploratory Development
- Clinical Development
- Pharmacovigilance
- Modeling & Simulation
- Toxicology
Available Guidance

- European Commission PIP Guideline
- ICH E 11 Guideline: Clinical investigation of medicinal products in the pediatric population
- EC Guideline: Ethical considerations for clinical trials conducted with the pediatric population
- EMEA Guidance
  - Formulations of choice for the pediatric population
  - Juvenile animals studies, Pharmacokinetics
  - Neonates, Pharmacovigilance, Small Populations
- EMEA Medicines for Children Website
Initial Considerations (based on ICH E 11)

- Prevalence in the pediatric population?
- Seriousness of the condition?
- Availability & suitability of alternative treatments?
- Medicinal product novel or known class properties?
- Unique pediatric indications?
- Need for pediatric-specific endpoints?
- Age ranges?
- Existing or anticipated safety concerns?
Time of PIP Submission

PIP required early in Development Process

- EU Pediatric Regulation, Article 16 1.

“….the pediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmaco-kinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC…”
Time of PIP Submission

PIP required early in Development Process

- PIP at availability of adult PK data

Concept and PIP

- PIP Modifications during Development Process
Pediatric Investigation Plan

*What the applicant has to address*

- **Product Information**
  - Type and details of the medicinal product
  - Regulatory information on clinical trials related to the condition and to the development in the pediatric population
  - Marketing authorisation status of the medicinal product
  - Advice from regulatory authorities
  - Orphan status in the EEA?
  - Planned application for
    - MA
    - Line extension
    - Variation
  - Annex of relevant documents
Pediatric Investigation Plan

What the applicant has to address

- Comparison between adults and pediatric age groups
  - Similarities and differences of disease/condition/effect of product
  - Prevalence and incidence in the pediatric population
  - Current methods of diagnosis, prevention and treatment
  - Significant benefit and fulfilment of therapeutic need

- Overall Pediatric Development Strategy
  - Indication(s), age groups, adult - pediatric development
  - Strategy for Formulation and for non-clinical and clinical program

- Planned measures for pediatric development, timelines
  - Outline of all steps and studies in development, study synopses
Practical Aspects

- Coordinated approach to PIPs, crossfunctional effort
  - for new products early, already in preclinical and phase 1
  - Epidemiology and medical need, existing therapies?
  - Pediatric Development?
  - Which indication, which age group, PIP, Waiver?
    - Identify external experts / advisory boards early
    - Seek pediatric advice for strategy and check of drafts

- Justification in detail strategy and all decided measures
  - Rationale for age ranges, timelines

- Estimation of workload and allocation of resources needed
First PIP Experience

- Two stage process with requests for modifications at d 60 e.g.
  - Age ranges  - e.g. request to study lower age range
  - Study design  - e.g. choice of endpoints
  - Formulation  - e.g. pediatric formulation issues
  - Safety aspects  - e.g. DSMB, more details on safety
  - Timelines  - e.g. longer study period, extension phase

- Clarification teleconferences and meetings

- Oral explanations at PDCO

- First positive PDCO opinions and EMEA decisions on PIPS and Waiver requests received
Waivers

Art. 11, EU Pediatric Regulation

- Waiver applications need good scientific justification
  - reference to 3 legal grounds in the Pediatric Regulation (Art.11)
    - (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the pediatric population
    - (b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations
    - (c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for pediatric patients
  - require detailed consideration and discussion of all age subsets
  - need significant work to cover all required information
List of Class Waivers

*Condition included in List of Class Waivers?*

**Short table of EMEA Class Waivers:**

Click on a column heading to sort alphabetically or by decision date

<table>
<thead>
<tr>
<th>Class of medicinal products</th>
<th>Condition</th>
<th>Decision date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxisome proliferator-activated receptor (PPAR)-gamma modulators, including dual and multiple PPAR modulators (e.g., thiazolidinediones, glitazars, triple modulators)</td>
<td><strong>Type II diabetes mellitus</strong></td>
<td>06/09/2008</td>
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<tr>
<td></td>
<td>Adenocarcinoma of the pancreas</td>
<td>21/04/2008</td>
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<tr>
<td></td>
<td>Gastric carcinoids</td>
<td>21/04/2008</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma of the colon and rectum</td>
<td>21/04/2008</td>
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<tr>
<td></td>
<td>Bladder carcinoma</td>
<td>21/04/2008</td>
</tr>
<tr>
<td></td>
<td>Liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)</td>
<td>21/04/2008</td>
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<tr>
<td></td>
<td>Chronic Obstructive Pulmonary Disease (COPD) (excluding chronic lung diseases associated with long-term airflow limitation, such as asthma, bronchopulmonary dysplasia, primary cilia dyskinesia, obstructive lung disease related to graft-versus-host disease after (bone-marrow) transplantation)</td>
<td>03/12/2007</td>
</tr>
</tbody>
</table>
Partial Waivers

- E.g. waivers for only specific age subsets
- For which age range PIP, for which age range waiver?
- Examples

<table>
<thead>
<tr>
<th>Example</th>
<th>Neonates</th>
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<th>Children</th>
<th>Adolescents</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
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<td>PIP</td>
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<tr>
<td>Infectious</td>
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<td>PIP</td>
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<tr>
<td>Diseases</td>
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Deferrals

Article 20, EU Pediatric Regulation

Deferrals can be requested for the initiation or completion of some or all of the measures set out in the PIP

- e.g. when it is appropriate
  - to conduct studies in adults prior to initiating studies in the pediatric population
  - or when studies in the pediatric population will take longer to conduct than studies in adults

Deferrals require at an early stage of product development

- a concept for potential pediatric development
- outline of measures and timelines as precise as possible
- justification of deferral
Example - Deferral of Initiation of Pediatric Program

- New product, adult development ongoing

- Pediatric Investigation Plan
  - Waiver request initially for 0-12 years, agreed upon up to age 10 years
  - Deferral for clinical study in 10-18 year old children/adolescents until after positive benefit/risk ratio in adults has been established

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<th>Children</th>
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<tbody>
<tr>
<td>New product</td>
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Evaluation procedure and Interactions with PDCO

- Predictable Timelines of PIP assessment procedure
  - Always according to schedule, no delays

- High level of Transparency
  - Detailed comments from EMEA coordinator, rapporteur and peer reviewer show assessment in a transparent way

- Good Communication
  - Opportunity of teleconferences for clarification of issues
  - Oral Explanation and Discussion at PDCO

- Pre-submission meetings? Program and PIP discussion during clock-stop before resubmission of revised PIP?
Global approach to Pediatric Drug Development

- Global needs – global programs, stepwise approach
  - 1. Pediatric Program Outline Preclinical/Phase 1
  - 2. EU PIP Process PK data & pediatric concept
  - 3. FDA Dialogue Phase 2/3
  - 4. PIP Modifications during Development process
  - 5. Goal: Global Pediatric Program

- Challenge: sometimes divergent views on, e.g. on
  - target population, age ranges, study design, endpoints

- Joint Pediatric Scientific Advise?

- Joint communication with FDA and EMEA during the PIP / WR and pediatric development process?
Conclusion

- The EU Pediatric Regulation requires routine assessment of pediatric drug development

- The Pediatric Investigation Plan is being integrated in Industry’s Drug Development Processes

- Pharmaceutical companies are actively implementing the EU Pediatric Regulation
  - PDCO has received 356 PIP and Waiver applications as of 12/2008
  - Number of pediatric studies will increase significantly
Conclusion

- Effective dialogue and collaboration between all stakeholders, including
  - Pediatricians
  - Medical and Patient organizations
  - EMEA, PDCO, FDA
  - Pharmaceutical companies

is essential for “Better Medicines for Children”
Thank you!