



The EU PIP - a step in Pediatric Drug Development

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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



Implications for Industry

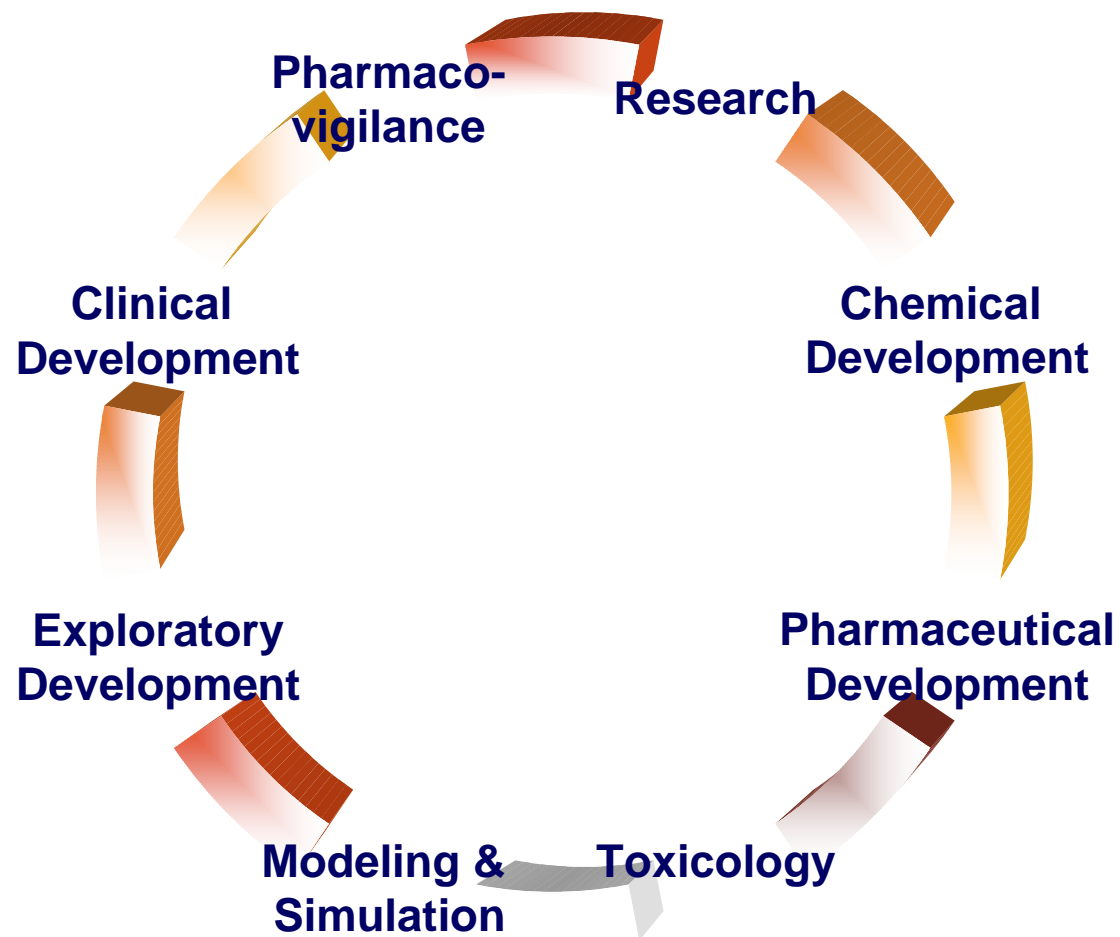
- Integration of pediatric aspects in development process
- Assessment of Product Portfolio for pediatric use
 - Marketed Products
 - All Products from early to late Development
- Pediatric Investigation Plans or waiver requests needed
 - for MAA of all new products since July 26, 2008
 - for new indications, 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



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.

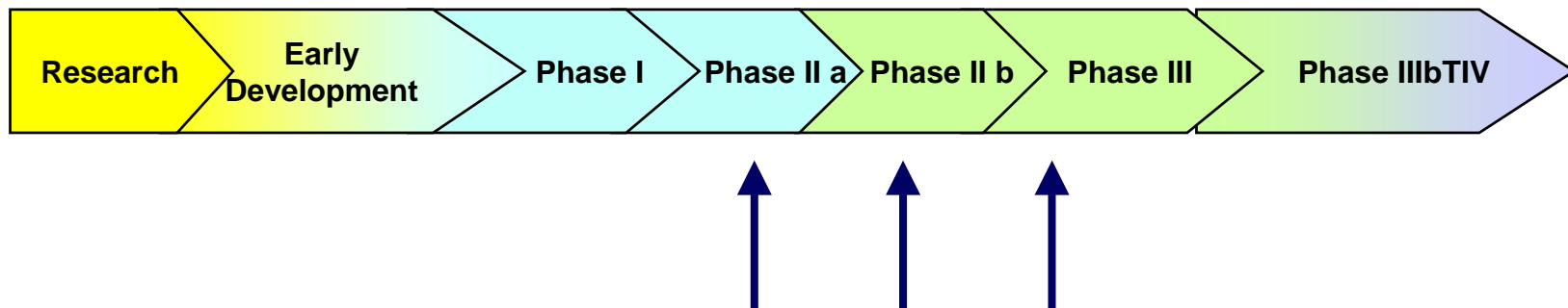
“....the pediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, **not later than upon completion of the human pharmaco-kinetic studies in adults** specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC...”

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

Class of medicinal products	Condition	Decision date
peroxisome proliferator-activated receptor (PPAR)-gamma modulators, including dual and multiple PPAR modulators (e.g., thiazolidinediones, glitazars, triple modulators)	type II diabetes mellitus	08/09/2008
	Adenocarcinoma of the pancreas	21/04/2008
	Gastric carcinoids	21/04/2008
	Adenocarcinoma of the colon and rectum	21/04/2008
	Bladder carcinoma	21/04/2008
	Liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)	21/04/2008
	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).	03/12/2007

Partial Waivers

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

Example	Neonates	Infants		Children	Adolescents
Cardiovascular	W	W ?	PIP	PIP	PIP
	W		PIP	PIP	PIP
Infectious Diseases	W	W ?	PIP	PIP	PIP
	W		PIP	PIP	PIP

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

Example	Neonates	Infants	Children	Adolescents
New product	W	W	W ?	Deferral
	W	W	W	Deferral

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 !

