Key concepts of the paediatric regulation and latest developments

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The EU Paediatric Regulation

I

(Acts whose publication is obligatory)

of 12 December 2006
(Text with EEA relevance)
Objectives of the EU Paediatric Regulation

• 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 authorization for adults
Paediatric development is now mandatory in the EU

• Unless a product-specific **waiver** or a class waiver is granted (which applies only for specific conditions and dosage forms)

• **Deferrals** can also be granted (studies in children can be initiated and/or completed after applying for marketing authorisation in adults)
Pillars of the Paediatric Regulation

- A system of OBLIGATIONS and REWARDS
- Paediatric Committee
- Paediatric Investigation Plan (PIP)
- Transparency / information measures
- Other measures
# EU Paediatric Regulation: obligations versus incentives

<table>
<thead>
<tr>
<th>Type of MP</th>
<th>Obligation</th>
<th>Incentive</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New Medicinal product</strong></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><strong>On Patent and authorized Medicine</strong></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><strong>Orphan Medicine</strong></td>
<td>Paediatric Investigation Plan or Waiver</td>
<td>2 additional years of market exclusivity*</td>
<td>In addition to 10 years</td>
</tr>
<tr>
<td><strong>Off patent Medicine</strong></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>

*if compliance with PIP, information, approval EU-wide
## Differences EU (Paediatric Regulation) / USA (BPCA-PREA-FDASIA)

<table>
<thead>
<tr>
<th>Development</th>
<th>US BPCA</th>
<th>US PREA</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Optional</td>
<td>Mandatory</td>
<td>Mandatory (optional for off-patent)</td>
</tr>
<tr>
<td>Instrument</td>
<td>Written Request</td>
<td>-</td>
<td>Paediatric Investigation Plan</td>
</tr>
<tr>
<td>Waiver</td>
<td>N/A</td>
<td>3 grounds</td>
<td>3 grounds</td>
</tr>
<tr>
<td>Timing</td>
<td>End of phase 2</td>
<td>End of phase 2</td>
<td>End of phase 1</td>
</tr>
<tr>
<td>Reward</td>
<td>6 months exclusivity</td>
<td>-</td>
<td>Main: 6 months SPC extension (patent)</td>
</tr>
<tr>
<td>New drugs (section 505)</td>
<td>Yes With exclusivity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Biologica ls (most)</td>
<td>Yes</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Orphan</td>
<td>Included</td>
<td>Excluded</td>
<td>Included</td>
</tr>
<tr>
<td>Decision</td>
<td>FDA</td>
<td>FDA</td>
<td>EMA (Opinion: Committee)</td>
</tr>
</tbody>
</table>
What is a PIP?

From the Paediatric Regulation (art. 2.2):

‘paediatric investigation plan’ means a research and development programme 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
Paediatric Investigation Plan

- Data on efficacy, safety and age-appropriate formulation are needed
- Timelines for start and completion of each study
- *In practice: discussion on each condition/indication and formulation, for each paediatric subset (not only age groups).*
Enabling SMEs to agree PIPs/waivers smoothly
Information on already agreed PIPs/waivers and on existing paediatric data

Or:

What can the EMA do for you?
Transparency / provision of information

EMA decisions on Paediatric Investigation Plans

- On EMA homepage (www.ema.europa.eu), and searchable
- Contains paediatric trials agreed between EMA and company (+dosage form and non-clinical studies)
- From 2013 will include “key elements” of each trial (short summary)
Database of all paediatric clinical trials performed before 2008 and not otherwise submitted to reg. authorities (authorised products)

- Art. 45: all existing paediatric studies to EMEA/NCAs by 26/1/2008
  - appr. 17,000 names of studies received
  - appr. 3,200 results of studies published on EMA website (http://bit.ly/10BPba7)
  - Appr. 3,200 results of studies received, still to be published
  - Evaluation ongoing (national products)
Paediatric clinical trials in EU-CTR

clinicaltrialsregister.eu/

- All clinical trials and of other trials submitted to National Authorities (protocol-related information)
- Third countries trials linked to a PIP
- Results will be added in EudraCT (Q4 2013)
- Access possible via WHO portal

- **Public access to paediatric information for authorised products** (EudraPharm)
Proceedings from Expert groups at EMA (http://tinyurl.com/PaedExpGroups)

Not binding for PDCO, but provide general guidance for PIP development

How to write a PIP - P Tomasi 2013
European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)

- Network of research networks
- EU and extra-EU
- EMA implementing strategy of the European network
- Stimulation of quality research in EU
- Annual workshop, meeting with industry
PIP/waiver presubmission meetings

- To be requested with sufficient advance (at time of Letter of Intent)
- Draft PIP application needed for discussion
- PDCO Rapporteur and Peer Reviewer always invited
- Scope is facilitation of validation and smooth procedure
Ultra-short course on how to prepare a PIP application

or: what has the Agency done to simplify life to applicants?

1) simplified forms (key elements) and opinions
2) New scientific document template (B-E)
3) predictable identification of the right condition (scope of the PIP)
4) How to claim the reward earlier (changing the scope of the PIP)
What to do first

Read the basics – do your homework!

• Paediatric Regulation http://bit.ly/tth2CD
• EC Guideline on Format and Content of PIP applications http://tinyurl.com/ECGuidancePIP
• EMA Procedural Advice http://tinyurl.com/PIPQ-A
• Other documents/guidelines
Other documents: Additional EMA Procedural Guidance

- All Templates and Deadlines for applications [http://tinyurl.com/PaedTemplatesDates](http://tinyurl.com/PaedTemplatesDates)
- Q&A on PUMAs [http://tinyurl.com/PUMAQ-A](http://tinyurl.com/PUMAQ-A), published in September 2011
- Guidance (2012) on:
  - Defining the scope of the PIP (“condition and indication”);
  - Changing the scope of PIPs (“merging” and “splitting” PIP decisions)
SIX CORE QUESTIONS

1. Is there a need for the candidate medicinal product in children?
2. If there is a need for paediatric development, what is the condition(s) in which paediatric development should occur, considering the proposed indication(s) in adults?
3. In which age group(s)/paediatric subsets should the development take place?
4. Should there be an adapted formulation and a specific non-clinical package?
5. What clinical measures should the paediatric investigation plan contain?
6. Should measures in the PIP (mainly clinical trials in children) be deferred or not?
Defining the scope of the PIP
(adult indication and relevant PIP condition)
How to identify the condition of potential paediatric need (scope of the PIP)

- Systematic approach based on 3 pillars:
  - proposed indication(s) and therapeutic area in adults
  - characteristics of the product (mechanism of action)
  - hierarchical classification of diseases/conditions
MedDRA hierarchical structure

- System Organ Class (SOC)
- High Level Group Terms (HLGT)
  - High Level Terms (HLT)
  - Preferred Terms (PT)
  - Low Level Terms (LLT)

(therapeutic areas)
(conditions)
(indications)
Principle: overarching HLT identified

Condition (HLT)

indication A (PT)
indication B (PT)
indication C (PT)
indication D (PT)
indication E (PT)
indication F (PT)
indication G (PT)

Step 1:
Applicant proposes indication C in adults

Step 2:
PDCO / Applicant identify HLT as condition of reference (MoA)

Step 3:
PDCO / Applicant identify indication F as best paed indication
Principal Steps

1. Analysis of proposed condition/indication / MOA

2. Determination of HLT *(HLGT or PT exceptionally)*

3. Discussion of Conditions (PTs) included under HLT

4. Determination of indication to be studied in PIP: 1 PT
   - Mechanism of action
   - Paediatric use / need
   - As close as possible to indication/condition targeted by applicant

5. PIP-opinion = HLT, automatically covering all PTs below HLT without further waiver(s) needed
Structure of the PIP application
(simplification of opinions)

- Section A: Product and Regulatory information
- Section B : Targeted conditions / indications and needs General pharmacology, Clinical need by age groups/subsets (with prevalence), Benefit of the product versus alternatives
- Section C : Waiver request
- Section D: Summary of existing data and Development plan Quality, Non-clinical, Clinical (±Risk management Plan), synopses of proposed non-clinical and clinical studies
- Section E: Timelines, deferral request

- Key elements form: applicant’s proposal for opinion

PDF form

Word document, free format

PDF form
Studies: what to put where

• Study synopses/outlines must be provided in PIP application for ALL studies of paediatric relevance, including pharmaceutical and nonclinical studies – AND DEFERRED STUDIES!

• Not (necessarily) a traditional full study protocol.

• From Feb 2013:
  • Put *proposed key elements* for the PIP opinion in the new “Key elements” PDF form (}

Simplified PIP opinions - P Tomasi 2013
New template for scientific document (parts B-E)

The template does not include tables for quality, non-clinical and clinical studies (applicant is free to use any format)
New template for scientific document (parts B-E)

The template however includes tables for modelling and simulation studies and for extrapolation studies, to guide on the level of detail.

<table>
<thead>
<tr>
<th>Modelling and Simulation Study Name</th>
<th>Insert here a descriptive name for the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Objective</td>
<td>Model objective/s must be specified. Choose from: Study, optimization, Data analysis, Does finding, Decision making.</td>
</tr>
<tr>
<td>Model Description</td>
<td>Type of model must be specified: Population PK / PD model, Physiologically based PK / PD model, Mechanistic model, Exposure response model.</td>
</tr>
<tr>
<td>Data to be used to Build Model</td>
<td>This must describe the type of data used to build the model. This includes data from: Literature, In vitro, Non-clinical, Adult and Paediatric data. Studies and literature references must be listed with the following format: Type of data (e.g. PK, PD, Clinical efficacy, Safety) Age subpopulation providing data, Number of patients/participants, Sampling time points (model could employ random sampling points), Number of samples per patient.</td>
</tr>
<tr>
<td>Model Building Methodology &amp; Software</td>
<td>This must describe the approach used to build model. Choose from: Step up (Physiologically based), Step down (Population based), Software used must be detailed.</td>
</tr>
<tr>
<td>Covariates</td>
<td>Provide a discussion on covariates. These must include at least: Age, Body Surface Area, and Weight.</td>
</tr>
<tr>
<td>Model Qualification</td>
<td>This must describe both the internal and external qualification used to validate the model assumptions and make adjustments.</td>
</tr>
<tr>
<td>Date of completion of study</td>
<td>Provide month and year/s a date is always necessary.</td>
</tr>
</tbody>
</table>

If modelling and simulation studies are planned as a substantial (or exclusive) part of the PIP, use the following format in this document. In the Key elements form (PDF file), please, list the key elements of substantial N/S studies using the clinical study table.

<table>
<thead>
<tr>
<th>Study Identifier(s)</th>
<th>Measure to extrapolate efficacy to the paediatric population</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study, study design</td>
<td>Analysis of existing in house and literature data on mechanisms/mode of action, class of medicines, and/or conditions.</td>
<td></td>
</tr>
<tr>
<td>Study objective(s)</td>
<td>To provide/supplement data on the paediatric population based on extrapolation. Perhaps add some specificities e.g. from source population.</td>
<td></td>
</tr>
<tr>
<td>Target population: Children aged from birth to less than 18 years of age.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methodology</td>
<td>To present data supporting the assumption that the outcome of treatment is likely to be similar in paediatric subsets by age and by any other relevant characteristics compared to adults.</td>
<td></td>
</tr>
<tr>
<td>To model and evaluate pharmokinetic, pharmacodynamic, response and efficacy data in adults and pharmokinetic data in children.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population and subpopulation definition (incl. stratification)</td>
<td>Disease, population description, disease done, registry, data source in adults.</td>
<td></td>
</tr>
<tr>
<td>Study population participates by paediatric subset (e.g., age, sex, stratification)</td>
<td>Number of study participants by paediatric subset (e.g., age, sex, stratification).</td>
<td></td>
</tr>
<tr>
<td>Date of initiation</td>
<td>Date of completion (last patient, last visit)</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>Paediatric Co-ordination</td>
<td></td>
</tr>
<tr>
<td>Rapporteur</td>
<td>&lt;Text&gt;</td>
<td></td>
</tr>
</tbody>
</table>
Key elements form

• Applicants should list here what their proposal is for the key elements of the opinion

• EMA/PDCO will use the proposal in the preparation and draft of the PDCO opinion
### Key elements form Clinical measure (trial)

**Clinical studies (currently 1 study)**

<table>
<thead>
<tr>
<th>Study is</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Type of control</td>
</tr>
<tr>
<td>Objective</td>
<td>Randomisation</td>
</tr>
<tr>
<td>Blinding</td>
<td>Minimum number of paediatric participants</td>
</tr>
</tbody>
</table>

**Summary of proposed clinical study, to be included in the PIP**

<table>
<thead>
<tr>
<th>PIP study number</th>
<th>13G1906420718</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Identifier (for referencing older studies)</td>
<td></td>
</tr>
</tbody>
</table>

**Main study design features and objectives**

**Study population and subset definition**

**Number of study participants by paediatric subset**

**Study duration for participants**

**Dose, treatment regimen, route of administration**

**Control(s)**

**Primary endpoint(s) with time(s) of assessment**

**Main secondary endpoint(s) with time(s) of assessment**

**Statistical plan including study conduct and analysis**

**Other**

**Plan for specific follow-up**

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**External Data Safety Monitoring Board (yes / no)**

<table>
<thead>
<tr>
<th>Date of initiation</th>
<th>Additional dependencies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferral for initiation requested? Yes No</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of completion</th>
<th>Additional requirements:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferral for completion requested? Yes No</td>
<td></td>
</tr>
</tbody>
</table>

Use the buttons below to add additional studies to the form.

- Add Quality Measures
- Add Non-Clinical Study
- Add Clinical Study
### Key elements form Clinical measure (trial)

- Hovering with the mouse over a field shows specific guidance

---

<table>
<thead>
<tr>
<th>Control(s)</th>
<th>Describe per treatment arm, e.g.:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end</td>
<td>“Group A: drug x, film-coated tablet (adolescents 12 years and older) or chewable tablet (children less than 12 years of age), 10 mg/kg daily”</td>
</tr>
<tr>
<td>Main second</td>
<td>If dosage unknown, specify on which basis the dosage will be selected.</td>
</tr>
<tr>
<td>Statistical</td>
<td>If applicable, specify wash-out, dose titration, taper down etc.</td>
</tr>
<tr>
<td>Other</td>
<td>Do not use acronyms like BID, always spell out (twice daily)</td>
</tr>
</tbody>
</table>

---

**Clinical studies (currently 1 study)**

**Summary of proposed clinical study, to be included in the PIP**

<table>
<thead>
<tr>
<th>PIP study number</th>
<th>1361906420718</th>
</tr>
</thead>
</table>

**Study Identifier (for referencing older studies)**

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</tr>
</tbody>
</table>

**Main study design features and objectives**

- Study population and subset definition
- Number of study participants by paediatric subset
- Study duration for participants
- Dosage, treatment regimen, route of administration

---

Plan for specific follow-up
The PDCO will then adopt an opinion using the simplified template

- Already in use since December 2012
- Reduced number of fields and simplification of details
- The website has the old version – to be updated soon
- The template for clinical studies key elements has only 13 fields
Changing the scope of the PIP
(“merging” and “splitting” PIP decisions for condition)
http://bit.ly/R2UERw
When is “merging” / “splitting” PIP decisions indicated?

• **“Merging”:** may be compulsory if regulatory application involves 2 or more conditions (routes, ph. forms) that are dealt in separate PIPs
  
  ✓ To comply with art 7/8 at MA/variation/LE application

• **“Splitting”:** always optional. Needed if company wants to (potentially) benefit from an earlier reward, for completing the PIP only for one condition (route, ph form), when the original agreed PIP included 2 or more

• In both cases: procedure of modification of agreed PIP necessary
Principle on requirement for single PIP decision (“merging” PIP decisions)

- The EMA will not accept in a regulatory application (or applications submitted at the same time) the submission of independent PIP Decisions (i.e. without cross-reference), as the tracking of such situations would be impossible to manage by the EMA or national competent authority.

- Multiple PIPs:
  - are possible
  - they may allow an earlier reward, but:
  - May not satisfy the requirement of art. 8 (PIP decision has to address existing and new indications, routes and ph. forms).
“Merging” PIP decisions

- Done via a procedure of modification of an agreed PIP (any of the existing ones) – but will be specified in the decision

- Other PIP decision still valid

- The “modified” PIP opinion does not change (unless modifications also for the existing PIP)

- Decision has new sentence:
  This agreed PIP covers all conditions, indications, pharmaceutical forms, routes of administration, measures, timelines, waivers and deferrals, as agreed in PIP EMEA-XXXXXX-PIPYY-ZZZZ(-M0X) (decision P/XX/20YY) including subsequent modifications thereof.
“Splitting” PIP decisions

- **PIP eligible for the reward (“reward PIP”):** the PIP which is triggered by the first regulatory procedure submitted by the applicant (after the first PIP is agreed)

- **PIP 1 containing conditions A and B:** modification procedure needed to remove either A or B from PIP

- If development is continuing for both (albeit not simultaneously): applicant to request new PIP for removed condition at the same time
Conclusion
“Everything should be made as simple as possible, but not simpler.”

Albert Einstein
Still uncertain?

- Call or write to your Paediatric Coordinator (EMA Scientific Administrator assigned to the procedure), or:
- Write to paediatrics@ema.europa.eu
- The friendly Paediatric Medicines team will answer
Backup slides
Bridging adults → children: “complete” vs. “partial” extrapolation

- Extreme view: anything less than 2 fully powered confirmatory trials is extrapolation
- “partial” extrapolation is highly prevalent, albeit unacknowledged. Examples:
  - One-sided vs. two-sided significance tests and/or higher p values allowed in specific situations
  - Bayesian methods
  - One confirmatory study only
  - No confirmatory study (orphan conditions)
  - Registration after failed superiority vs placebo (but superiority vs active comparator demonstrated)
5-year results of Paediatric regulation

More studies in children

- % paed CTs over total CTs
- %CTs including children in EudraCT
- N. of CTs incl. children in EudraCT
- % of paediatric CTs that are in PIPs (MCRN UK)
5-year results of Paediatric regulation
More medicines for children

• Linked to Paediatric Regulation (centrally / nationally):
  – 13 new medicines for paediatric use (10 / 3)
  – 30 new paediatric indications (18 / 12)
  – 9 new pharmaceutical forms relevant for children (3 / 6)

• Incentives:
  – Supplementary protection certificates extended in 16 Member States concerning 11 medicines
  – 1 PUMA only (1 ongoing)

• PIPs are progressing without reported issues in >50%

• Good overlap between agreed PIPs and off-label use (survey)
Main roles of PDCO

- **To adopt opinions on PIP/waivers** (decision signed by EMA Executive Director, not by EU Commission)

- **To provide advice on any question relating to paediatric medicines** (at the request of the Agency's Executive Director or the European Commission)

- **To assess data generated in accordance with agreed PIP, to adopt opinions on the quality, safety or efficacy of any medicine for use in the paediatric population** (at the request of the CHMP or a national competent authority)
When should the PIP be requested?

- Non-clin
- Phase 1
- Phase 2
- Phase 3
- Post approval

Paediatric Investigation Plan

(PIP Amendments)

Compliance check

Paediatric Committee (PDCO)
Deferral(s):

Instrument to avoid delaying marketing authorisation in adults

“Deferred” means Marketing Authorisation Application for adults is possible before initiation/completion of one or more measures in the PIP

• Given by study/measure (cfr US PREA: “total” deferral)
• For initiation and/or completion of study/measure: completion of a clinical trial may be deferred, but initiation may not be!
• Completion dates established
Paediatric Use Marketing Authorisation

- New dedicated type of Marketing Authorisation application (MAA) for exclusive paediatric use
- Intended for off-patent medicinal products:
- Incentives:
  - 10 year marketing protection (compliance with agreed PIP necessary) on data contained in the PUMA
  - Fee reductions for Marketing Authorisation
- Studies funded by European Commission (Framework Programme), chosen from a priority list of off-patent drawn by EMA (public private partnership, 75 m€ so far)
PUMA

- Results so far rather disappointing
- 25 to 35 PIP applications for possible PUMA
  (difficult to say as PIP application for new product + possible PUMA not identifiable)
- 3 PUMA applications so far
- Incentive is weak (data protection + market protection) and limited to the paediatric data