The New Paediatric Regulation - Establishment and Role of the Paediatric Committee (PDCO)

DGRA.e.V Bonn
June 2007

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CHMP Chair / EMEA
Plan

- Legislative Process
- Paediatric Committee (PDCO)
- Paediatric Investigation Plan (PIP)
- Interactions
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Legislative Initiative

- First European publications in the 80’s
- European Commission Round Table, EMEA, December 1997
- European Council Resolution in Dec 2000
- Consultation and Extended Impact Assessment 2000-2004
- Adoption of Draft Regulation by European Commissioners in September 2004
Paediatric Medicines Were Still not Studied

Number of active substances: 258 (1995 - January 2006)

- 24% Paediatric indication
- 32% Potential paediatric indication
- 44% Not applicable

EMEA data
Legislative Process

- Vote in European Parliament, 1 June 2006

- Publication of Regulation expected December 2006
- Entry into force January 2007 but staggered implementation
Objectives of the 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 authorisation for adults
Main Pillars

- Creation of a Paediatric Committee at EMEA
- Measures for patented medicinal products
- Measures for off-patent medicinal product
For yet Unauthorised Products

Patent-protected products

- Obligation to submit **results of agreed** Paediatric Investigation Plan at time of marketing authorisation, or variation (i.e. new indication, route of administration, or pharmaceutical form)

- Reward
  - 6 months extension of the Supplementary Protection Certificate (= patent protection)
For ‘Old’ Products

Off-patent products not covered by a patent or supplementary protection certificate

- Optional procedure
- Paediatric Use Marketing Authorisation (PUMA)
  - Paediatric Investigation Plan needed
  - Formulation + paediatric indication(s) only
Old products (2)

Incentive

- 10 years data protection/exclusivity (as for new products)
- Possible use of existing brand name (brand recognition)
15-20% of rare diseases affect children only, 55% affect adults and children

**Reward**

2 years of market exclusivity added to existing 10 years, if development in accordance with Paediatric Investigation Plan
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COMPOSITION:

5 CHMP members
+
22 members per Member State not yet represented
+
6 members from families & HCP associations

Each member has an alternate
Paediatric Committee

- 6 months to establish (i.e. before July 2007)

- Expertise in all aspects related to medicines for children
  - Pharmaceutical development
  - Paediatric medicine
  - General practitioners
  - Paediatric pharmacy
  - Paediatric pharmacology
  - Paediatric research
  - Pharmacovigilance
  - Ethics and public health
Tasks of PDCO (1)

- Paediatric Investigation Plans (more than 200 announced in 2007)
  - Assessment (on basis of EMEA summary report)
  - Deferrals
  - Modifications

- Waivers (more than 80 announced in 2007)
  - Product and condition (severity?)
  - Public list of waivers

*About 300 procedures from questionnaire to EMEA MAH/MAA, but likely to be more as not all companies have understood the scope*

- Compliance checks
Tasks of PDCO (2)

Use as Expert Group by and for CHMP

- Scientific Advice (158 announced in 2007)
  - No paediatric expertise in SAWP
  - Duplication of expertise to be avoided
  - Use of PEG has proved useful but limited number of experts for areas covered, and workload

- ‘SAG’ or expert source for marketing authorisation applications (60-70% of new products with paediatric interest)
Tasks of PDCO (3)

- Paediatric Needs Inventory: Criteria for survey of use (off label) by Member State

- Support and Advice on the European Network establishment

- Experts for DG Research? (FP7 funding)
Tasks of PDCO (4)

- Advice on “communication of arrangements available for conducting research into medicinal products for paediatric use”, which corresponds to Eur. Parliament’s wish for PDCO to promote participation in/educate on clinical research
- Advice to Commission, or to EMEA Executive Director on an ad-hoc basis
- Opinion on symbol for paediatric products
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  - Submission
  - Timing
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Paediatric Investigation Plan

- Basis for the development and authorisation of a medicinal product for the paediatric population subsets
- Include details of the timing and the measures proposed to demonstrate
  - Quality
  - Safety
  - Efficacy

+ Any proposed adaptation of the medicinal product

Marketing Authorisation Criteria
COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF APPLICATIONS FOR AGREEMENT OR MODIFICATION OF A PAEDIATRIC INVESTIGATION PLAN AND REQUESTS FOR WAIVERS OR DEFERRALS AND CONCERNING THE OPERATION OF THE COMPLIANCE CHECK AND ON CRITERIA FOR ASSESSING SIGNIFICANT STUDIES

Comments should be e-mailed as word documents using the template to Peter Arlett at the European Commission (peter.arlett@ec.europa.eu)
Paediatric Investigation Plan (PIP) indication:

- The proposed indication(s) in the paediatric population for the purpose of a PIP and at time of PIP submission
- It should specify if the medicinal product is intended for diagnosis, prevention or treatment of a condition
Definitions

*Proposed therapeutic indication:* The therapeutic indication in adults and/or paediatric populations as proposed by the PIP applicant at the time of submission of the PIP.

*Granted therapeutic indication:* The therapeutic indication in adults and/or paediatric populations that is included in the MA. This will be the result of the assessment of the Q/S/E data submitted with the MA application.
Definitions

ICH E11

- Birth - 27 days: pre-term and term neonate
- 1 month (28 days) - 23 months: infant
- 2 years - 11 years: child
- 12 years - 17 years: adolescent
  up to 18th birthday

Subsets
- Can differ, but the use to be justified
Principles

1. Same application (form) for PIP/Waiver/Deferral/Combination

2. Applications to cover all subsets of the paediatric population

3. Applications (Article 8) to cover all existing and new indications but in one PIP

4. All relevant information (+ or – to the product) to be included in the dossier, in particular incomplete/discontinued pharmaco-toxicological test/CT

5. The assessment of
   • Significant therapeutic benefit
   • Fulfilment of therapeutic needs

to be assessed in the light of any other relevant information
Administrative and Product Information (1)

Part A

1. Name, address of the applicant (contact person)
2. Name of manufacturer (of active substance/medicinal product)
3. Name of active substance (INN)
4. Type of product (chemical, biological, vaccine... / target, mechanism of action)
5. Details (strength, form, route of administration...)

Administrative and Product Information (2)

Part A

6. Regulatory status in the EU
   - MA status (including refusals)
   - Authorised indications/routes/dosage forms
   - Information on CTs within EU
   - Scientific advices (SAWP – National)
   - Restrictions (in any EEA...)

7. Regulatory status outside EU (including refusals)
   - Worldwide
   - Adult/Paediatric
   - Any third advice of any type in third countries on paediatric development
Administrative and Product Information (3)

Part A

8. Conditions according to ICD – IO
9. Proposed therapeutic indication (+ATC code)
Overall Development Information on Target Diseases/Conditions

Part B

1. Discussion on similarities/differences between populations (adults versus paediatric [subsets])

2. Discussion on anticipated similarities/differences on the effect of the product (adults versus paediatric [subsets])

3. Prevalence/incidence in the paediatric population


5. Significant therapeutic benefit, fulfilment of therapeutic need (decision to go for a PIP/waiver)
Basis for Significant Therapeutic Benefit

a) Improved efficacy upon the existing
b) Substantial improved safety profile
c) Better dosing scheme/method of administration
d) Availability of relevant age-appropriate formulation
e) New/relevant clinical knowledge of better use
f) Different mechanism of action

- At this (early) stage of development, such claims could be based on ‘well justified’ and plausible assumptions
- If not, consider waiver/deferral
- Refer to the inventory when appropriate
Applications for Waivers

Part C

1. Scope
   - Age range/subsets
   - Pharmaceutical form
   - Route of administration

2. Grounds
   - Based on efficacy/safety (justify lack of E/S risks)
   - Based on condition/disease (in adults ‘only’!?)
   - Based on lack of significant therapeutic benefit
PIP

Part D1

Overall strategy proposed by the applicant:

- Indication
- Selected age groups
- Outline of the quality/(non)-clinical data
- Extrapolation/interrelation between adult/paediatric
- Existing paediatric information
- Significant therapeutic/fulfilment of therapeutic need
Strategy in Relation to Quality

Part D2

- Need for a specific formulation/dosage form in relation to age group
- Availability/timeframe of the formulation/dosage form
- Appropriateness to age subsets (device, food...) (suitability)
Strategy in Relation to Non-clinical Aspects (S)

Part D3

- **Pharmacology**
  - Proof of concept
  - PD studies
  - Safety pharmacology

- **PK**
  - Juvenile animals

- **Toxicology**
  - Juvenile animals (species)
  - Specific endpoints (neuro-, nephro-, tox...)
  - Local tolerance (topical...)
Strategy in Relation to Clinical Aspects (E)

Part D4

Appropriateness of clinical endpoints

- **PD**
  - Difference adults/paediatrics
  - Extrapolations
  - Need for specific studies
  - Biomarkers(?) for PK(?) , for PD(?)

- **PK**
  - Extrapolations from adults/older groups
  - Bridging studies (adults/older groups)
  - Need for specific studies
  - Population PK
  - Interactions (?) possibility to extrapolate, effects of pharmacogenetics
Strategy in Relation to Clinical Aspects (E)

Part D4

Appropriateness of clinical endpoints

- Efficacy/safety studies
  - Dose finding studies
  - Relevance of age-appropriate endpoints
  - Use of surrogate markers
  - Need short/long term safety studies
  - Need for studies in the post-authorisation phase

- Technicalities
  - Less invasive techniques
  - SMB
  - Recruitment
Planning for Development

Part D5

1. Overall summary table (all studies)
2. Outline of each study/steps in development
3. Synopsis of protocols of non-clinical
4. Synopsis of protocols of clinical
   - Type of study/control
   - Design
   - Location
   - Test product/regimen/route
   - Number of subjects
   - Duration of treatment
   - Main in-exclusion criteria
   - Endpoints
   - Sample size/power calculations
   - Recruitment issues, interim analyses...
   - Statistical methods
Timeline of Measures in PIP

Part D6

- Detailed timelines
- Compared to the adult development
- Predicted timing of applications
- Timelines of initiation/completion of each measure
Deferrals

Part E

- Specify indication/route/form
- Specify age group to which it applies
- Justify
  - Conduct in adults prior to the paediatric population
  - Longer duration in paediatric populations
  - Need for additional non-clinical data
  - Difficulties to develop timely a relevant formulation
Request of PIP

PIP
± report
± Partial Waiver

PDCO
YES
New

PIP
± report
± Partial Waiver

PIP
± report
± Partial Waiver

Full Waiver

REFUSAL

PDCO
NO

Full waiver = no reward
Request for Waiver

Full waiver = no reward
Annexes

Part F

- References of published literature
- Investigation brochure
- Previous opinions on competent authorities
- Information of an authorised product
Amendments of PIP

The same template to followed, mentioning the changes in the relevant sections.
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  - Checks
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Timing Consultation of PDCO

Scientific Advice

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

Amendments PDCO

Compliance
## PIP Procedure

<table>
<thead>
<tr>
<th>Step</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-submission meeting Intent to file</td>
<td>- 3 months</td>
</tr>
<tr>
<td>Validation &amp; preparation of Summary Report by the EMEA</td>
<td>30 days</td>
</tr>
<tr>
<td>Opinion PDCO on PIP</td>
<td>60 days</td>
</tr>
<tr>
<td>Optional extension</td>
<td>60 days</td>
</tr>
<tr>
<td>Opinion to applicant</td>
<td>10 days</td>
</tr>
<tr>
<td>Request for re-examination</td>
<td>30 days</td>
</tr>
<tr>
<td>FINAL decision EMEA</td>
<td>10 days</td>
</tr>
<tr>
<td>TOTAL</td>
<td>200 days</td>
</tr>
</tbody>
</table>
Overview PIP Procedure

1st discussion PDCO Day 30

2nd discussion PDCO + OE Day 60

Stop Clock

Update Sum Report

Adoption of Opinion

60 DAYS

Day 1 After Validation, Sum Report

Adoption of Opinion or List of Issues

Start Clock

Day 61

3rd discussion PDCO Day 90

Oral Explanation

60 DAYS

~ 3 months
Example for Discussion

Paediatric Committee Established

Decision PIP

1st submission PIP: Validation & Assessment & Decision 30+60+50 d

Studies following agreed PIP & preparation application ?

Compliance Up to 60 d with PDCO

MAA Assessment minimum 150-210 days

EC Decision 44 days

Application SPC-extension 6 months before expiry

Before 07/2007

Not before 07/2009

Compliance Up to 60 d with PDCO

Variation application Assessment Minimum 90 days

EC Decision 44 days

Application SPC-extension 6 months before expiry

Not before 01/2009

Compliance Up to 60 d with PDCO

EC Decision 44 days

Application SPC-extension 6 months before expiry

Before 07/2007

Not before 07/2009
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Compliance Check

‘The compliance check includes whether all measures agreed in the PIP decision have been conducted in accordance with it, including the agreed timelines.’

Non-compliance will lead

- Non-validation of applications falling under Art. 7, 8
- For validated applications, non-inclusion in the MA of the compliance statement, thus ineligibility for the rewards and incentives
Compliance Check (C.C)

- Only a fully completed PIP can be checked for compliance
- Amendments are no long possible at the time of the C.C
- Stopping a PIP (for safety reasons...) should lead to an amendment or waiver in front of the PDCO before any C.C
- C.C is not linked to any scientific judgement/assessment of data (Q, S, E)
Compliance Check

- **Step 1 (At Validation)**
  - By competent authority (reference MS)
  - By PDCO at EMEA (60 day procedure)
  - Before or during Validation MAA

- **Step 2 (During Assessment)**
  - Checking facts

- **Statement on Compliance**
  - For granting of rewards and incentives

Guidance, training and learning from experience
(feed back from Competent Authorities)
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SAWP and PDCO

- Scientific Advice: non binding
- Adults and children development
- Fee attracting procedure (adults, non orphan)
- Reduced fee for SME
- Free for orphan (Protocol Assistance) and paediatric indication

- PIP decision is binding on company
- Paediatric development only
- No fee
PDCO & Scientific Advice (SA)

Request SA → Q, S, E Paediatrics

SAWP

Meeting Discussion

Experts

SAWP

CHMP

Final SA

Experts

Experts PDCO

Experts PDCO
Publication of PDCO Opinions and EMEA Decisions

- Legal requirement to publish opinions and decisions after deletion of commercially confidential information
- Under discussion
- No publication of detailed PIP
- Waivers
- Timelines of initiation and completion
Summary

- Regulation 1901/2006
- Guidance EU-Commission PIP
- EMEA action Plan implementation
- PDCO
- Development of Research/Clinical Investigations
- Perspectives of Paediatric Indications after July 2008
Conclusions

• A 7-year process but real achievements
• Regulatory framework for Europe
• A major change in the way medicines are developed
• Better medicines for the children of Europe
Thank You
Abbreviations

- EMEA: European Medicines Agency
- EU: European Union
- ICH: International Conference on Harmonization
- Council: Council of Ministers (Council of European Union)
- PIP: Paediatric Investigation Plan
- CHMP: Committee on Medicinal Products for Human Use
- PUMA: Paediatric Use Marketing Authorisation
- PK: pharmaco-kinetics
- EUDRACT: European Database of Clinical Trials
- FP7: 7th Framework Programme
European Medicines Agency

www.emea.europa.eu

DG Enterprise website

pharmacos.eudra.org

- Paediatric regulation proposal and explanatory texts
- Latest version (link)
- Guideline on Ethics