EU Paediatric Regulation
One Year PDCO

Bonn, DGRA
June 2008

Daniel Brasseur
PDCO at the EMEA
Paediatric regulation

of 12 December 2006

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission

(4) This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in
Plan

- Committee
- PIP submissions
- PDCO assessment
- Perspectives
COMPOSITION:
5 CHMP members
+ 1 member per Member State not yet represented
+ 6 members from families & HCP associations
Each member has an alternate
COMPOSITION:

5 CHMP members

1 member not yet

6 members

& HCP

Each member has an alternate

Link with CHMP reps!

1 Missing ... Alternates

No Family, HCP rep yet!
Plan

- Committee
- PIP submissions, Procedure
- PDCO assessment
- Perspectives

Achievements & Challenges
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)

Not published yet
Practical aspects on how to submit an application for paediatric investigation plan and requests for waiver and deferral

I. Letter of Intent ................................................................. 1
II. When to submit the application ........................................... 1
III. Paediatric Investigation Plan/Waiver application ..................... 1
   III.1 Electronic template of the application ............................. 1
   III.2 Practical Information about the electronic template ............. 2
   III.3 Guidance to fill in the information requested in the application form ..................................................... 2
   III. 4 Guidance for the scientific documentation .......................... 4
IV. Requirements concerning the electronic submission ..................... 4
V. Where to submit the application? ........................................... 4
VI. Number of copies ............................................................ 5
   VI.1 Cover letter to be submitted together with the application ............... 5
**PIP Procedure ‘Intention’ Phase**

- **Day -60** Rapp/PeerR designations
- **Day -70** Company’s Letter of intent
- **Day -30** Company’s PIP Application
- **Day 0** Preparation EMEA SmR & List of Issues

- **40 DAYS**
- **30 DAYS**

- **EMEA Validation Period**
- **First Wave 60 DAYS**

**Start Clock**
Preparation EMEA SmR & List of Issues
Day -60 Rapp/PeerR designations

Day -60 Rapp/PeerR designations
Day -30 Company’s Letter of intent
Day –30 Company’s PIP Application
Day 0 Start Procedure

40 DAYS EMEA Validation Period

Preparation EMEA SmR & List of Issues

Start Clock First Wave 60 DAYS

List of Issues

Expertise & Efficiency
PIP Validation & Summary Report

Day -60 Rapp/PeerR designations

Day -70 Company’s Letter of intent

Day -30 Company’s PIP Application

Preparation EMEA SmR & List of Issues

List of Issues

EMEA Validation Period

Day 0 Start Procedure

Start Clock

First Wave 60 DAYS

40 DAYS

Expertise & Efficiency
Plan

- Committee
- PIP submissions
- PDCO assessment

Timing

- Perspectives
Overview PIP Evaluation

Adoption of Opinion

Start Clock 60 DAYS Decision

Expertise & Efficiency
Overview PIP Evaluation

Adoption of Opinion, or Request for Modification

Start Clock

60 DAYS

Stop Clock

Expertise & Efficiency
Overview PIP Evaluation

Adoption of Opinion, or Request for Modification

Start Clock

60 DAYS

Stop Clock

ReStart Clock

60 DAYS

Opinion

Understand Plan
Detect Problems
Identify Experts
Propose Modifications

Expertise & Efficiency
Overview PIP Evaluation

Opportunity for the Company to introduce Modifications

Expertise & Efficiency
Overview PIP Evaluation

Start Clock

60 DAYS

Stop Clock

ReStart Clock

60 DAYS

Decision

Evaluate Changes
Find Agreement
Finalize Plan
Publish Decision

Expertise & Efficiency
Plan

- Committee
- PIP submissions
- PDCO assessment Outcome
- Perspectives
- Alzheimer's Disease
  Based on the ground of onset of symptoms
  Disease occurs earlier
- Vascular dementia
  Based on the ground of onset of symptoms
  Vascular dementia is a common condition and the average age of onset is 65 years
- Organic amnesic syndrome
  Based on the ground of onset of symptoms
  Alcohol and other psychoactive drugs are involved
- Amyotrophic lateral sclerosis
  Based on the ground of onset of symptoms
  Reported in the 2nd decade
- Parkinson's disease
  Based on the ground of onset of symptoms
  Parkinson's disease usually occurs in the age of 40 years
- Age-related macular degeneration
  Based on the ground of onset of symptoms
  The average age of onset is 50 years
- Menopausal and other hormone-related conditions
  Based on the ground of onset of symptoms
- Complications associated with chronic obstructive pulmonary disease
  Based on the ground of onset of symptoms
- Chronic Obstructive Pulmonary Disease (COPD)
  Based on the ground of onset of symptoms
  Chronic Obstructive Pulmonary Disease (COPD) may develop in patients with chronic respiratory diseases associated with smoking such as primary cilia dyskinesia and graft-versus-host disease, etc.
- Treatment of adenocarcinoma of the pancreas
- Treatment of gastric carcinoids
- Treatment of adenocarcinoma of the colon and rectum
- Treatment of bladder carcinoma
- Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma)
- Treatment of kidney and renal pelvis carcinoma (including nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney)
- Treatment of melanoma
- Treatment of gastric adenocarcinoma
- Treatment of chronic lymphocytic leukaemia
- Treatment of cervix and corpus uteri carcinoma
- Treatment of follicular lymphoma
- Treatment of primary osteoarthritis (excluding secondary osteoarthritis)
- Treatment of coronary atherosclerosis
- Treatment of peripheral atherosclerosis
- Treatment of Huntington's disease
- Treatment of benign prostatic hyperplasia
- Treatment of erectile dysfunction
- Treatment of primary gout (excluding Lesch-Nyhan syndrome and other secondary forms of gout)

Multiple myeloma
Based on the ground that the condition does not normally occur in the paediatric population. Multiple myeloma median age of diagnosis is 71 years (Cancer, principles and practice of oncology 7th edition) and only 1% of cases occur before the age of 40. No incidence rates are reported.

Adopted Nov. 23 2007
Updated April. 21 2008


Oncology

- Pancreatic cancer
- Hepatocellular carcinoma
- Gastric carcinoids
- Colon and rectum cancer
- Bladder cancer
- Liver and intrahepatic bile duct cancer
- Kidney and renal pelvis cancer
- Melanoma of the skin
- Stomach cancer
- Trachea and bronchus cancer
- Chronic lymphatic and chronic myelotic leukaemias
- Cervic uteri cancer
- Follicular lymphoma
Plan

- Committee
- PIP assessment, Scientific grounds
- PDCO assessment
- Perspectives
Main Questions...

Has the candidate medicinal product:

1. any interest for children?
2. in which condition(s)?
3. in what age range(s)?
4. under which form(ulations)?
Examples

- HTA in children SBP, DBP, MBP???
- Cancer: PFS? QoL?
- Paediatric Diabetes study design?
  - add-on therapy on top to metformin/compared to metformin?
  - non-inferiority design (sample size)
  or
  superiority design against placebo/diet with metformin as internal control?
Growth

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME
RECORD #

Maturation

Safety

Girls
Boys

Expertise for Paediatric Drug Development
Achievements
Ongoing submissions

<table>
<thead>
<tr>
<th>Total number of validated PIP / waiver applications</th>
<th>2007 (August to December)</th>
<th>2008 (January-May)</th>
<th>Cumulative Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>85</td>
<td>113(^1)</td>
<td>198(^2)</td>
</tr>
<tr>
<td>Applications submitted for a product not yet authorised (Article 7(^{[v1]})(^3)</td>
<td>39</td>
<td>85</td>
<td>124 (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 (Article 8)</td>
<td>45</td>
<td>23</td>
<td>68 (34%)</td>
</tr>
<tr>
<td>Applications submitted for an off-patent product developed specifically for children with an age-appropriate formulation (Article 30)</td>
<td>1</td>
<td>5</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>PIPs and full waiver indications covered by these applications</td>
<td>202</td>
<td>159</td>
<td>361</td>
</tr>
</tbody>
</table>
## Achievements Opinions

<table>
<thead>
<tr>
<th>Number of Paediatric Committee (PDCO) opinions</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on full waiver</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Positive on PIPs including potential deferral</td>
<td>2</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Negative Opinions adopted</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
**PIP applications**

**EMEA received after 9 months of activities**
(by submission deadline 14.04.2008)

Number of indications covered
in the requests for PIPs or waivers: 361
  *including full waivers*
  *for the paediatric development*
  *for the whole indication* 45

but considering for partial, as an average 4 age classes:
- waiver *or*
- deferral *or*
- ‘kick-off’
- premature/nesonates
- infants
- toddlers/school-age children
- teenagers or adolescents

**Coordination & Collaboration**
PIP Distribution

Article 7
New medicinal products (not yet authorised) 124 63%

Article 8
Medicinal product under patent 68 34%

Article 30
Off-patent medicines developed specifically for paediatric use with an appropriate formulation 6 3%
Areas covered by PIPs / waivers

- Neurology 12%
- Gastroenterology-Hepatology 10%
- Pneumology – Allergology 8%
- Infectious Diseases 11%
- Cardiovascular Diseases 14%
- Endocrinology-Gynaecology 18%
- Immunology–Rheumatology 4%
- Oncology 11%
- Vaccines 3%
Plan

- Committee
- PIP submissions
- PDCO assessment
- Perspectives Interactions
PDCO interactions CHMP WPs

Comments Revisions Updating Additions

EWP Group PK
SWP Guidelines
QWP Formulations
VWP Neonatal
CHMP
CAT
Non-clin Phase 1 Phase 3 Post approval

Amendments Compliance
Investigation Plan PDCO

Coordination & Collaboration

Inside EMEA
PDCO Activities A team approach

Academic Institutions

National Networks

EU Networks

European Experts

Assessor Team

Rapporteur Peer R

Paediat Board

NCA

EMEA

Coordination & Collaboration

EU National Networks
Plan

- Committee
- PIP submissions
- PDCO assessment
- Perspectives
  Communication policy

Achievements & Challenges
OVERVIEW PIP PROCEDURE

Provisional Opinion, & Request for Modification

Adoption of Opinion & Final Report

Start Clock

60 DAYS

Stop Clock

ReStart Clock

60 DAYS

Opinion

Decision

Withdrawal

Withdrawal

Withdrawal

Withdrawal

Withdrawal

Withdrawal

Nothing in public Domain
Re-examination

- ReStart Clock
  - 60 DAYS
- Opinion 1
- Appeal
- Opinion 2
- 30
Re-examination

ReStart Clock

60 DAYS

Opinion 1

30

Opinion 2

10

Decision

‘Appeal’

Adoption of Opinion & Final Report
Re-examination

- ReStart Clock
- 60 DAYS
- Opinion 1
- 30 DAYS
- Opinion 2
- 10 DAYS
- Appeal Decision

1st Opinion mentioned in public Domain

- Decision
- Withdrawal
Conclusion

- Workload as expected, even more...
- Timely Deliverables at the cost of...
- Fantastic Team Work at the EMEA!

- Continuous Motivation to act for ‘free’
- Renewed Expertise to assess Novel Fields
- Need to simplify, clarify & dialogue
Conclusion

• Fantastic Team Work
• Workload as expected, even more...
• Timely Deliverables at the cost of...

• Continuous Motivation to act for ‘free’
• Renewed Expertise to assess Novel Fields
• Need to simplify, clarify & dialogue
PDCO Activities A team approach
Overview PIP Evaluation

- Start Clock
- First Wave 60 DAYS
  - Rapporteur’s written Contribution Day 20
  - 1st Rapp Oral Present. at PDCO Day 30
  - 1st Discussion PDCO +OE? Day 60
- PDCO Opinion
- EMEA Decision
  - Peer Reviewer’s Comments Day 27
  - Members’ written Comments Day 30-55
  - Update EMEA/ PDCO Final Report Day 60

OE= oral explanation
Steps of PIP Evaluation

- Rapporteur’s written Contribution Day 20
- 1st Rapp Oral Present. at PDCO Day 30
- 1st PDCO Discussion +OE? Day 60
- Peer Reviewer’s Comments Day 27
- Members’ written Comments Day 30-55
- Update EMEA/PDCO Report Request for Modification

First Wave 60 DAYS

Stop Clock

Re-Start Clock 2nd Wave 60 DAYS

OE= oral explanation
Steps of PIP Evaluation

Re-Start Clock

Company’s PIP Re-Submission Day 61
EMEA Sm Report Update Day 71
2\textsuperscript{nd} Rapp Oral Present. Day
& 2\textsuperscript{nd} PDCO Discussion +OE? 90

2\textsuperscript{nd} Wave Days 61-120

Rapporteur’s Comments on Modifications Day 80
PRreviewer’s Comments on Modifications Day 88
Members’ Final Comments to EMEA Day 105

3\textsuperscript{rd} PDCO Discussion Final Report Day 120

PDCO Opinion

Update EMEA/PDCO Sm Report Day 110

EMEA Decision

EO= oral explanation
Steps of PIP Evaluation

1st Discussion PDCO Day 30

2nd Discussion PDCO Day 60

3rd Discussion PDCO Day 90

4th Discussion PDCO Day 120

Start Clock

60 DAYS

Stop Clock

ReStart Clock

60 DAYS

Day 1 After Validation EMEA Sm Report

Adoption of Opinion, or Request for Modification

Day 61 Re-Submission EMEA Update Sm Report

Adoption of Opinion & Final Report

~ 3 month

OE= oral explanation

Expertise & Efficiency
EMEA/PDCO SUMMARY REPORT

on an application for

a

Paediatric Investigation Plan

including a request for a deferral

and a request for a waiver

for

<table>
<thead>
<tr>
<th>PIP Procedure</th>
<th>Date</th>
<th>Procedure Day Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report version 0 from EMEA</td>
<td>01/08/2007</td>
<td>1</td>
</tr>
<tr>
<td>Report version 1 from Rapporteur</td>
<td>20/08/2007</td>
<td>20</td>
</tr>
<tr>
<td>Report version 2 from Peer-reviewer</td>
<td>28/08/2007</td>
<td>28</td>
</tr>
<tr>
<td>Report version 3 with comments from PDCO</td>
<td>13/09/2007</td>
<td>44</td>
</tr>
<tr>
<td>Report version 4 from EMEA</td>
<td>25/10/2007</td>
<td>61</td>
</tr>
<tr>
<td>Report version 6 with comments from PDCO</td>
<td>20/12/2007</td>
<td>120</td>
</tr>
</tbody>
</table>

The PDCO Rapporteur for the application were appointed at the PDCO Meeting
PDCO Rapporteur: Prof. Paolo Rossi
Peer Reviewer: Prof. Johannes Taminiau
EMEA Paediatric Co-ordinator: Dr. Annic Weyersberg