10 Years of Pediatric Regulation in EU - EMA

PMDA Symposium, 2016 Nov 28

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Head of Portfolio Board, Head of International Affairs a.i.
Visiting Expert at PMDA (2016 Oct-Nov)
Acknowledgements

The Pediatric Office at EMA (especially Chrissi Pallidis and Gunter Egger)
The EMA Paediatric Committee
The children and their parents...

Chair: Dr Mentzer
The pillars of the 2006 EU Pediatric Regulation:

- Paediatric Committee
- Pediatric Investigation Plans/Waivers
- Pediatric Network
- Transparency
A system of obligations and rewards

- New medicines (and new indications, new route of administration, new pharmaceutical forms) must have an agreed Pediatric Investigation Plan (PIP) or a Waiver to be submitted for Marketing Authorization
- Submission of PIP or Waiver request no later than “completion of adult PK studies” (generally understood as end of phase 1)
- Reward is 6-month extension of the ‘Supplementary Protection Certificate’ (=EU patent extension, length variable, not available to all medicines)
- Voluntary process for off-patent medicines

Goals of the Pediatric Regulation:

1. More medicines for children
2. Better Product Information
3. More Pediatric Trials and Research
More pediatric medicines - Achievements 1

- Medicines: 97
- Indications: 141
- Dosage forms: 29

2007-2015
New medicines of pediatric relevance

* Indications where there were no approved pediatric medicines

• Rheumatology
  • 14 PIPs leading to 8 pediatric indications

• Cardiovascular Diseases
  • Several anti-hypertensives and cholesterol-lowering agents (same)

• Anti-infectives
  • Several antivirals, antibiotics and anti-fungals

• Pediatric oncology
  • First for neuroblastoma, and new less toxic regimens

* Indications in age groups where there were no treatments approved
More information on pediatric medicines – Achievements 2

- Information on pediatric dosing: 316
- Information on pediatric study results in product information: 261
- Information on safety of pediatric medicines: 201
- Other information: 689
More information on pediatric medicines – Achievements 2

Paediatric Regulation entry into force

Section of the SmPC: 4.3 4.4 4.5 4.7 4.8 4.9 5.1 5.2 5.3

Number of authorised products

Year

2004 2005 2006 2012 2013 2014

5.3 Non-clinical
5.2 PK
5.1 PD
4.9 Overdose
4.8 ADR
4.7 Effects on driving
4.5 Interactions
4.4 Warnings
4.3 Contraindications
International Perspective (2007-2015*)

<table>
<thead>
<tr>
<th>Region</th>
<th>EU</th>
<th>US</th>
<th>Japan</th>
<th>Canada</th>
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<tbody>
<tr>
<td>New pediatric medicines</td>
<td>80*</td>
<td>76</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>New pediatric indications/dose</td>
<td>141*</td>
<td>173</td>
<td>38</td>
<td>107</td>
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<tr>
<td>Total</td>
<td>221</td>
<td>249</td>
<td>50</td>
<td>145</td>
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*different reporting period
Paediatric Committee workload (2007-2015)

**Pediatric Investigation Plans**
- 859 approved
- 11 refused
- 42 Waivers

**Modifications**
- 1.2 / PIP on average

**PIP completed in compliance**
- 100

**Waivers**
- 379 approved
- 39 refused
Pediatric Investigation Plans and Deferrals

- Most new medicines get a deferral (of trials) until after adult development
- Deferral of between 5-10 years, some beyond 10 years
- Feasibility/recruitment issues but also lack of investment
- Sequential development (older groups studied first, neonates last) intended to protect against unknown toxicity:
  - No real evidence of protection
  - Persistent off-label use in neonates....
  - To be abandoned!
Submission of existing pediatric trial results

Submission either to EMA for centrally-approved medicines, or to National Agencies for nationally-approved medicines

**Article 45**
- Submission of any existing pediatric trial completed before 2007

**Article 46**
- Submission of completed pediatric trial within 6 months of completion (after 2007)
Submission of existing pediatric trial data

Trials with centrally-approved medicines

- EMA CHMP
  Committee for Human Medicines
- Assessment

Trials with nationally-approved medicines

- CMD(h)
  Committee for Human Mutual/ Decentralised Procedures
- Assessment/work sharing

Recommendations: New pediatric indication, New product information, No change
# More information on pediatric trial results – Achievement 2

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<thead>
<tr>
<th></th>
<th>Article 45</th>
<th>Article 46</th>
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<tbody>
<tr>
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<td>Centrally approved</td>
<td>Nationally approved</td>
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<tr>
<td>Reports*</td>
<td>199</td>
<td>~19,000</td>
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<td>Active substances</td>
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<td>~1,000</td>
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<td>Assessments</td>
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<td>219**</td>
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<td>New indication</td>
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<td>Other changes</td>
<td>10</td>
<td>~140</td>
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</table>

*more than one report per study  **ongoing  ~not exhaustive

2007-2015

Arch Dis Child. 2016 Jan;101(1):81-4
More research into pediatric medicines

- Ethical safeguards of pediatric clinical trials (2008 EU guideline, under revision)

- Network of pediatric networks (collaborative research)
  Enpr-EMA, Neonatal Consortium

- More/larger pediatric clinical trials (in particular involving neonates)

- Funding of research into off-patent medicines

- International Collaboration for global pediatric development (Cluster, Networks)
More pediatric research – Achievements 3

Clinical Trials in <18 Y (source EU-CTR)
Transparency

• Transparency of pediatric clinical trials in EU database (incl. trial results)
• Article 45 database
• Publication of Pediatric Committee opinions/EMA Decisions on PIPs and Waivers
• Publication of Agendas and Minutes of Pediatric Committee
• Other EMA initiatives on Transparency
Conclusions

The EU Pediatric Regulation has delivered significant and relevant outcomes over the last 10 years:

- More medicines for children
- More information on medicines
- More clinical trials

There are improvements to be made to make the system more efficient

- Fewer but more focused PIPs, with for example rolling evaluation
- Need for pediatric oncology and neonatal medicines solutions
Thank you for your attention

Further information
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