The 10 year EMA report on the EU regulation with a focus on oncology

5th Annual Paediatric Oncology Conference

Presented by Koenraad Norga & Franca Ligas on 2 March 2017
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Background

Regulation (EC) No 1901/2006
2007: entry into force

Objectives:

• Increase ethical high-quality research into medicines for children
• Increase availability of authorised medicines for children
• Increase information on medicines for children

Achieve the above:

- Without unnecessary studies in children
- Without delaying authorisation for adults
Paediatric investigation plan

‘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’

Article 2 (2) of Regulation (EC) No 1901/2006
## Therapeutic areas of agreed PIPs (2007-2015)

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Number of agreed PIPs</th>
<th>Number of completed PIPs</th>
<th>Completed/a agreed PIPs</th>
<th>Number of authorisations of paediatric indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthesiology</td>
<td>3</td>
<td>0</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>48</td>
<td>9</td>
<td>19%</td>
<td>6</td>
</tr>
<tr>
<td>Dermatology</td>
<td>33</td>
<td>5</td>
<td>15%</td>
<td>5</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>13</td>
<td>2</td>
<td>15.4%</td>
<td>1</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>12</td>
<td>3</td>
<td>25%</td>
<td>1</td>
</tr>
<tr>
<td>Endocrinology/metabolic diseases</td>
<td>70</td>
<td>7</td>
<td>10%</td>
<td>6</td>
</tr>
<tr>
<td>Gastroenterology/hepatology</td>
<td>33</td>
<td>5</td>
<td>15%</td>
<td>4</td>
</tr>
<tr>
<td>Haematology</td>
<td>46</td>
<td>3</td>
<td>6.5%</td>
<td>1</td>
</tr>
<tr>
<td>Transplantation</td>
<td>10</td>
<td>2</td>
<td>20%</td>
<td>1</td>
</tr>
<tr>
<td>Immunology/rheumatology</td>
<td>46</td>
<td>14</td>
<td>30.4%</td>
<td>8</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>17</td>
<td>2</td>
<td>12%</td>
<td>2</td>
</tr>
<tr>
<td>Vaccines</td>
<td>37</td>
<td>9</td>
<td>24.3%</td>
<td>9</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>17</td>
<td>2</td>
<td>12%</td>
<td>2</td>
</tr>
<tr>
<td>Neurology</td>
<td>45</td>
<td>3</td>
<td>7%</td>
<td>2</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>96</td>
<td>14</td>
<td>15%</td>
<td>14</td>
</tr>
<tr>
<td>Neonatology/paediatric intensive care</td>
<td>16</td>
<td>1</td>
<td>6%</td>
<td>1</td>
</tr>
<tr>
<td>Oncology</td>
<td>83</td>
<td>7</td>
<td>10%</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>9</td>
<td>1</td>
<td>11%</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonology/allergy</td>
<td>35*</td>
<td>7</td>
<td>20%</td>
<td>6</td>
</tr>
<tr>
<td>Uro-nephrology</td>
<td>16</td>
<td>1</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Orthopaedic diseases</td>
<td>9</td>
<td>1</td>
<td>11%</td>
<td>0</td>
</tr>
<tr>
<td>Allergens*</td>
<td>114</td>
<td>0</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>808</strong></td>
<td><strong>98</strong></td>
<td><strong>12%</strong></td>
<td><strong>71</strong></td>
</tr>
</tbody>
</table>

Note: *Allergen PIPs assessed in 2010-2011 due to a change in regulation in Germany are listed separately here.
Source: EMA database (PedRA)

### ONCOLOGY End 2016:
- **93 PIPs (>50 mechanisms of action)**
- **10 PIPs completed**
- **5 Paediatric indications**
New medicines for children: before and after the Paediatric regulation

Number of new paediatric products, indications and posology
2004-2006 and 2012-2014

Paediatric Regulation entry into force

Year

2004 2005 2006 2012 2013 2014

Number

45 40 35 30 25 20 15 10 5 0

New paediatric products New paediatric indications New paediatric posology

The 10 year EMA report on the EU regulation with a focus on oncology
Centrally authorised anti-cancer medicines
## Class-waiver revision (July 2015)

<table>
<thead>
<tr>
<th>Paediatric development waived</th>
<th>Previous class waiver CW/1/2011</th>
<th>Revised class waiver CW/0001/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>For any medicine within a certain condition</td>
<td>• 44 conditions (including 22 cancers)</td>
<td>• 8 conditions (no cancer)</td>
</tr>
<tr>
<td>For specific classes of medicines within a certain condition</td>
<td>• 2 classes of medicines that are likely unsafe in children and that are used to treat 1 condition in adults</td>
<td>• 2 classes of medicines that are likely unsafe in children and that are used to treat 1 condition in adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 8 classes of medicines that are likely ineffective in children and that are used to treat 9 conditions (cancers) in adults</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 10 classes of medicines for which further studies in children are not justified and that are used to treat 14 conditions (including 11 cancers) in adults</td>
</tr>
</tbody>
</table>

Source: EMA website.
Incentives and rewards


- 39 medicines* in 23 Member States: Six-month extensions of Supplementary Protection Certificate

  ✓ 1 oncology product (Imatinib-Glivec)

- 6 orphan medicinal products: Two-year extension of the market exclusivity period (2016)

- 3 PUMAs: 10-year data protection

* + 3 in 2016 in 9 Member States
Comparison with other regions


<table>
<thead>
<tr>
<th>Region</th>
<th>EU</th>
<th>US</th>
<th>Japan</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>New paediatric medicines</td>
<td>80</td>
<td>76</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>New paediatric indications</td>
<td>141</td>
<td>173</td>
<td>38</td>
<td>107</td>
</tr>
<tr>
<td>Total</td>
<td>221</td>
<td>249</td>
<td>50</td>
<td>145</td>
</tr>
</tbody>
</table>

Note: EU data include CAPS and national/DCP/MRP products. Medicines exempt from paediatric obligations have been excluded from data provided by other regions (e.g. generics)
Networking & activities in paediatric oncology

- Pediatric cluster (monthly teleconference with EMA, FDA, HC, PMDA, TGA;) (~120 virtual meetings)

  ✓ *FDA and EMA : ~ 10 „ Oncology Common commentaries“ (SIOP 2016, Poster)*

- Oncology cluster (monthly teleconference with EMA, FDA, HC, PMDA, TGA; adult and paediatric assessments and advices)

- PRIority MEdicines scheme (PRIME) & Cross-commitees activities @ EMA

- Multi-stakeholder paediatric oncology strategy workshop (cancers with ALK aberrations), EMA, 30-31 January 2017

- Planned revision of the “Paediatric addendum” to the Guideline for evaluation of anti-cancer medicinal products in man.
Lessons learned - obligations & rewards

- Obligations and rewards → effective, but...

- Rewards not sufficient:
  - Not linked to development costs, efforts (e.g. interesting for statins/blockbusters, less so for lower volume/revenue medicines)
  - Not granted in some cases (or too late)
  - Require Supplementary Protection Certificate to have been granted (national, different expiration dates, 2 years mandatory notice...)

11 10-year Report to EC on the Paediatric Regulation
Lessons learned – Paediatric needs not yet met

- PIPs not always matching disease burden (Disability-adjusted-life-years*)
  - Mental/behavioural disorders highest burden 20% → only 3% of PIPs
  - Neonatal conditions, burden 14% → only 2% of PIPs
  - Infectious diseases, burden 5% → 21% of PIPs
  - Malignant neoplasms, burden 5% → 13% of PIPs

- Diseases unique to children still neglected
- Cancer unique to children still neglected

* time-based measure which combines years of life lost due to premature mortality and years of life lost due to time lived in state of less than full health (WHO)
Lessons learned – voluntary applications

- Conditions: Development linked to adult indication → missed opportunities for paediatrics

- Voluntary development → not a reliable model to address paediatric needs:
  - PUMA: Only three Paediatric Use Marketing Authorisations (PUMA) so far
  - 73 confirmations of applicability of class waiver (2011-2014), potential paediatric interest for 50 (68%) → but only one PIP submitted
  - Non-deferred studies tend to be completed in time and in compliance with the agreed PIP, deferred studies tend to be delayed
Lessons learned – Delays in completing paediatric studies

• Objective difficulties (prevalence, logistic, ethical...)
• Lack of return on investments
• Unwillingness of developers
• Deferrals (postponement of studies) accepted by PDCO:
  ✓ Too many and too generous? But: need to prevent delay of marketing in adults, and ensure some safety information is available
  ✓ Lack of effective enforcement mechanisms in case of non-compliance with the agreed date of completion of the PIP studies
Conclusions

- Paediatric oncology research is now often part of pharma development plans for anti-cancer medicines
- More research (number of trials, number of collaborations, number of networks on a global scale, etc.)
- Increased level of trust and transparency among all the stakeholders raising expectations for more developments
Acknowledgments

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Thank you for your attention

Further information

[Insert relevant information sources or contact details as applicable.]

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Back-up slides
Other activities for paediatric oncology

Overview of recommendations on PRIME eligibility requests by 26/01/2017 by therapeutic area

- All advanced therapies
- 3 with potential paediatric indications
- 1 paediatric studies before adult studies
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