Towards Successful Paediatric Orphan Medicines Development

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// Address unmet medical need in rare and paediatric diseases

// Address unmet medical need with PIPs based on Mechanism of Action (from adult-centric to child-centric approach) and understand the way how diseases are defined

// Procedural changes to support paediatric development
Call for a European Action Plan on Rare Diseases
(11th European Conference on Rare Diseases and Orphan Products)

Extract from open letter to Commissioner Kyriakides

The rare disease community needs a coordinated, cross-border and cross-sector European action plan on rare diseases. This call, reiterated by this letter, comes from all stakeholders: from patient advocates, clinical and research groups, industry umbrella:

- a strong European Health Data Space that upholds strong ethical principles of digital health and that includes a specific rare disease codification standard;
- the regulatory system positions the EU as a global leader in medicine development to address the unmet needs of the rare disease community;
- European Reference Networks improve standards of care by being well integrated into national health care systems through the upcoming joint action;
- Rare disease research is prioritised …, need to be cross-border but also cross-sector working with strong links between research, data and healthcare.
PROPOSAL 6: EURORDIS and EFPIA call for a Moonshot for basic and translational research for adult and paediatric rare disease:

- **Develop science for rare diseases**, thus supporting innovation in underserved areas. Typically, a Moonshot refers to an open-science model aimed at making knowledge generated from scientific research transparent and accessible through shared collaborative networks.

- **Establish a mindset of concerted effort** towards developing the basic science and accelerating the translational research that are prerequisites for clinical development.

- **Better coordination** of basic research, investment, and infrastructures.

- Built on public-private partnerships, leveraging existing initiatives such as the IMI and its successor, the Innovative Health Initiative (IHI), enabling collaboration opportunities for industry in any Commission programme dealing with rare diseases (e.g., ERNs for rare disease and potential European Rare Disease Partnership in Horizon Europe).
Some PPPs* to Advance Paediatric Research

Innovative trial designs, e.g. Master Protocol
Use of RWD, Big Data, Artificial Intelligence, MIDD, DCTs ...

*Public Private Partnerships

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Obligations and rewards under the provisions of the Paediatric Regulation

A pharmaceutical company develops a medicine targeting a specific condition in adults.

Childhood diseases have specificities which need to be taken into account during drug development. In line with the Paediatric Regulation, the company needs to develop the same medicine for children. A Paediatric Investigation Plan (PIP) is agreed with the European Medicines Agency (EMA) for every medicine in development, unless a waiver is granted. The PIP describes the company development strategy i.e. how and by when data will be generated for use of the medicinal product in children.

Developing specific medicines for children requires a great deal of effort from the companies. This is why the legislators have designed a set of rewards to compensate for the additional effort incurred.

- **PIP Waiver:**
  - medicine is not safe or effective for children;
  - medicine is not expected to be of use in children;
  - condition targeted by the medicine in development does not exist in children.

- **A 6-month extension to the supplementary protection certificate (SPC) for the product.**

  or

  If the product is an orphan medicinal product, the 10 years of market exclusivity provided by the Orphan Regulation can be extended by a further 2 years in the specific orphan indication.
Creating an innovation ecosystem to foster research into medicines for children

The upcoming review of the Paediatric Regulation provides an opportunity to evolve from an ‘adult-centric’ approach to a ‘child-centric’ approach. EFPIA proposes to:

Address paediatric Unmet Medical Needs (UMN) via Mechanism of Action (MoA) PIPs

EFPIA is proposing a framework for the "MoA PIP", based not on the adult indication, but on a paediatric unmet medical need. In other words, the PIP will be designed having in mind how the product works (its mechanism of action) and what unmet need in children it might be able to address. This would mean that a medicine developed for an adult disease may also be studied in a different childhood disease because both diseases have the same cause, and the treatment may work for both. This child-centric PIP approach implies significant efforts and scientific challenges. An additional reward for developers would be fair and appropriate.
Revision of how to define a condition (disease)

**Definition of Condition based on current scientific knowledge**

Thanks to advances in science, we are now able to understand the pivotal causes of many diseases. This is a game changer to discovering new treatments: many medicines are now developed to target the cause of a given disease.

The mechanism of action (MoA) of such a medicine can make it suitable for use in more than one condition if each condition can be shown to be associated to the same pivotal cause. We therefore propose to adjust how a disease (or a condition) is defined, to include the cause of the disease, where this link is scientifically proven based on the most up to date evidence.

**Better integrate paediatric development discussions into the overall regulatory development dialogue with regulators**

Discussions with regulators should also include the data generation needs for paediatric patients. Usually, these discussions also need input from other regulators such as the FDA to achieve alignment on a global paediatric programme.
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Submission of a Paediatric Investigation Plan (PIP) no later than upon completion of adult pharmacokinetic studies, and agreeing at this time what the paediatric development will be:

This is feasible when there is already sufficient prior information on the new medicine and the condition it will treat.

In other cases, we propose:

- An integrated paediatric development dialogue within the scope of the continuous regulatory dialogue discussions during product development

- An optimised PIP procedure with opportunities for dialogue and simplification to ensure best use of available resources
Key challenges for Paediatric Investigation Plans in rare paediatric diseases

At the time the PIP needs to be submitted many aspects of the development are not clear:

★ Limited understanding of the disease itself, especially also in the paediatric age ranges
★ Very limited in rare diseases and diseases often highly heterogenous

Would benefit from cross functional discussions initially to align on broad direction and feasible approach → exploring innovative design and extrapolation ideas with potential involvement of patient groups

★ Endpoints often need to be developed/established during drug development
  • Unclear whether endpoints for adults will/can be the same endpoints as for paediatrics
  • Clear understanding often at the end of proof-of-concept study or even phase 3 study
★ Limited understanding of the safety and efficacy of development product
★ No regulatory precedence available: standard of care, endpoint, agreed PIP etc.
Streamlining of Key Elements (KE)

**Key elements are:**
- The binding components of an agreed Paediatric Investigation Plan (PIP)
- Captured in the EMA decision associated with a PIP
- Basis for compliance check

**Considerations for streamlining the Key elements:**

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<tr>
<th>Focus primarily on the “What” rather than the “How”</th>
<th>Reduce the level of detail in KE</th>
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<td>→ directing discussions on the most significant aspects of a program</td>
<td>→ Details are discussed in the PIP scientific document and ultimately captured in other documents e.g. clinical protocols and associated marketing authorization documents</td>
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| Link dates and milestones to activities and interdependencies, rather than including specific dates |

**Aim:** reduce unnecessary PIP modifications and enable better utilization of resources
Evolutionary PIP concept

- PIP body will describe the data that is available to fill key elements
- Will be updated as data are available to fill the missing key elements
- Milestone elements are phrased to enable evolutionary data generation
Implementation of CT Regulation – More opportunities for Integrated Development Discussions Throughout Assessments

**Paediatric Plan (PIP)**
*What must be done?*
EMA Paediatric Committee (PDCO) responsibility

**Paediatric Scientific Advice**
*How is it done?*
EMA Scientific Advice Working Party responsibility (Quality/Safety/Efficacy)
PDCO experts involved

**Paediatric Clinical Trial (CTA)**
*How are CTs safe for participants; set up to answer the scientific questions; ethical?*
National Competent Authorities (NTA)/Clinical Trial CG/Ethics Committees responsibility
Should involve PDCO experts

**Paediatric Data (MAA)**
*Is the medicine safe and effective in children?*
EMA Committee for Medicinal Products for Human Use (CHMP)/NTA responsibility
Should involve PDCO experts
Multiple steps:

Close collaboration for more basic research, open science-model (“Moonshot”), inclusive infrastructures and data sharing

Child-centricity through Mode of action PIPs and

Science-based definition of conditions

Knowledge-based PIPs (“evolutionary PIPs”) and continuous involvement of paediatric expertise throughout the medicine development and regulatory assessments

To reach one goal:
More medicines against rare and paediatric diseases