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.

Open letter: ECRD partner organisations call on the European Commission for a new European strategy on rare diseases - eurordis.org

EFPIA-EURORDIS

Joint Statement on Patient Access to Medicines for Rare Diseases

6 Proposals with 5 mainly around access

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).

EFPIA-EURORDIS Joint statement on Patient Access to Medicines for Rare Diseases

Some PPPs* to Advance Paediatric Research

Integrated DEsign and AnaLysis of small population group trials

conect 4children
COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

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

InSPiRe
Innovative methodology for small populations research

SCREEN 4CARE

asterix

EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

Pre-Clinical → Clinical

RDCA-DAP®
Rare Disease Cures Accelerator
Data and Analytics Platform

*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

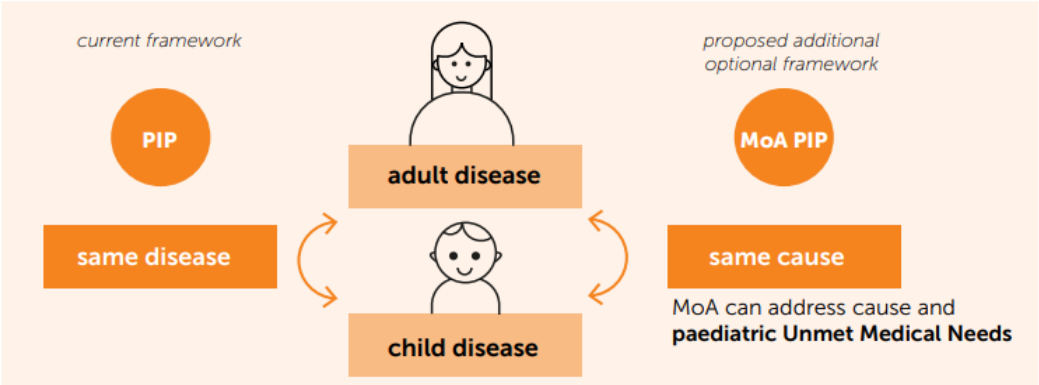
If the product is an orphan medicinal product, the **10 years of market exclusivity** provided by the Orphan Regulation can be **extended by a further 2 years** in the **specific orphan indication**.

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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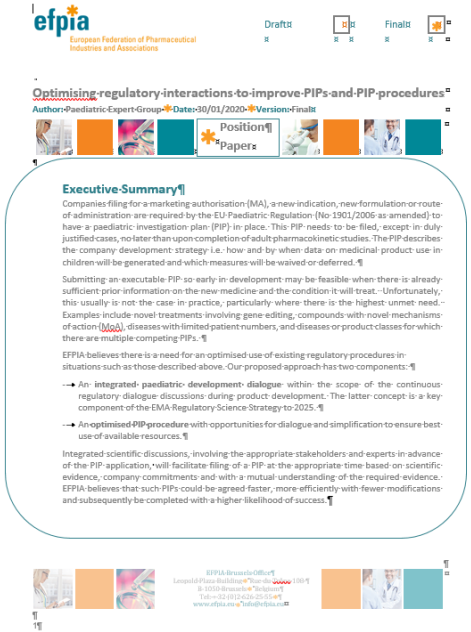
- **Procedural changes to support paediatric development**

Optimising regulatory interactions to improve Paediatric Investigation Plans and PIP procedures


efpia
European Federation of Pharmaceutical Industries and Associations

Draft Final

Optimising regulatory interactions to improve PIPs and PIP procedures

Author: Paediatric Expert Group Date: 30/01/2020 Version: Final

Position Paper

Executive Summary

Companies filing for a marketing authorisation (MA), a new indication, new formulation or route of administration are required by the EU Paediatric Regulation (No 1901/2006 as amended) to have a paediatric investigation plan (PIP) in place. This PIP needs to be filed, except in duly justified cases, no later than upon completion of adult pharmacokinetic studies. The PIP describes the company development strategy i.e. how and by when data on medicinal product use in children will be generated and which measures will be waived or deferred.

Submitting an executable PIP so early in development may be feasible when there is already sufficient prior information on the new medicine and the condition it will treat. Unfortunately, this usually is not the case in practice, particularly where there is the highest unmet need. Examples include novel treatments involving gene editing, compounds with novel mechanisms of action (MoA), diseases with limited patient numbers, and diseases or product classes for which there are multiple competing PIPs.

EFPIA believes there is a need for an optimised use of existing regulatory procedures in situations such as those described above. Our proposed approach has two components:

- An integrated paediatric development dialogue within the scope of the continuous regulatory dialogue discussions during product development. The latter concept is a key component of the EMA Regulatory Science Strategy to 2025.
- An optimised PIP procedure with opportunities for dialogue and simplification to ensure best use of available resources.

Integrated scientific discussions, involving the appropriate stakeholders and experts in advance of the PIP application, will facilitate filing of a PIP at the appropriate time based on scientific evidence, company commitments and with a mutual understanding of the required evidence. EFPIA believes that such PIPs could be agreed faster, more efficiently with fewer modifications and subsequently be completed with a higher likelihood of success.

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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:

Focus primarily on the **"What"** rather than the "How" → directing discussions on the most significant aspects of a program	**Reduce the level of detail** in KE → Details are discussed in the PIP scientific document and ultimately captured in **other documents** e.g. clinical protocols and associated marketing authorization documents	**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