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Optimising regulatory interactions to improve PIPs and PIP procedures

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✱ 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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Table of contents

1. Introduction

EFPIA would like to pro-actively contribute to the success of the 2018 EMA/EC paediatric action plan[1] and recommends an optimisation of regulatory interactions to improve both the PIPs and the procedures used for requesting and modifying PIPs. This proposal focuses on improving regulatory interactions within the context of the full development strategy of the product and is expected to facilitate more efficient and predictable development and speed up authorisation of new medicines for children based on robust scientific evidence.

Our proposal is fully workable within the current legislative framework, and optional. It will also help re-focus limited Health Authority resources to ensure their allocation to the most appropriate activities during medicine development, to support programs with the most added value. It takes into account the evolving scientific environment and the understanding of the concept of "disease"[2], particularly in therapeutic fields such as oncology, when tissue-agnostic and biomarker-driven therapies may become more relevant, as well as new ways of generating evidence.

Optimised regulatory interactions are especially useful for development programs for which major challenges or technical barriers might exist, such as the following:

- Compounds where the MoA is not fully characterised ('first-in-class') or treating/preventing a newly defined disease or indication with no approved product ('first-in-disease')
- Standard of Care (SoC) has recently changed or is divergent within the EU or between the EU and other countries
- Generation of the required evidence is challenging or requires discussion, e.g. patient scarcity, extrapolation or innovative trial designs
- Diseases with limited preclinical models
- Medicinal products created using gene editing, e.g. to repair or suppress a specific gene
- Tissue-agnostic therapies.

[1] https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

[2] As discussed in the Pharmaceutical Committee (point 2. Ii in https://ec.europa.eu/health/sites/health/files/files/committee/ev_20191217_785_en.pdf


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The proposed optimised regulatory interaction model has two components, both based on existing regulatory procedures:

- Component 1: 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[3].
- Component 2: an **optimised PIP procedure** with opportunities for dialogue and simplification to ensure best use of available resources.

Development discussions within the whole (adult and paediatric) development context will allow sufficient time and multiple opportunities to discuss key aspects in advance of the PIP filing and therefore facilitate subsequent regulatory PIP procedures.

2. Component 1: integrated paediatric development dialogue[4]

Medicine development is a high-risk and long-term commitment. Developers carefully design development programs to avoid failures and increase the probability of success for medicines to reach patients. Important development decisions are mainly driven by three factors: scientific opportunity, unmet medical need and expected value of a new medicine. Hence, global paediatric development strategies must be planned based on robust evidence and early conversations with regulators globally.

Discussions in the context of Scientific Advice (SA) or some other form of early dialogue platform should occur before PIP submission and should continue until there is agreement on the most appropriate paediatric development strategy for the medicinal product. Paediatric development dialogue should be integrated and function within a single-entry platform (a 'one-stop-shop') for developers to consult European regulators on any medicinal product development question. These discussions are voluntary, but it is important that sufficient resources are available to increase critical scientific dialogue as needed.

Each development program is different, but all programs belong somewhere between the two extremes below, with very different development risk profiles:

(1) Paediatric development fully linked to the adult indication, and safety and efficacy in children may be determined through extrapolation from adult data and pharmacokinetic and safety studies in children

[3] https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-2025 in particular https://www.ema.europa.eu/en/documents/presentation/presentation-ema-regulatory-science-2025-diversify-integrate-provision-regulatory-advice-along_en.pdf

[4] Please note detailed proposals for Component 1 will be captured in a separate paper [in preparation].


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(2) Paediatric development completely independent from the adult indication, and requires substantial independent data generation to prove safety, quality and efficacy in targeted paediatric age-groups.

Integrated advice could be useful in all cases but is expected to particularly benefit development programs where scientific data need to be generated in adults before subsequent development strategies can be decided.

Integrated scientific discussions, involving the appropriate stakeholders and experts in advance of the PIP application, would allow the filing of a PIP at the appropriate time and based on scientific evidence, company's commitments and with a mutual understanding of the required evidence

Firstly, the SA or early dialogue platform should allow involvement of relevant experts from the European Regulatory Network, EMA Committees (CHMP, PDCO and other relevant committees, e.g. COMP) and EMA staff depending on the applicant's specific questions. It also should allow involvement of patients and health care professionals and in particular, paediatric networks, to achieve patient-centric development strategies that address unmet medical needs with a feasible operational plan. Discussions should be held early and within the context of the global development program to address important aspects of the paediatric development strategy, including relevant age groups and conditions, potential extrapolation, formulation requirements, juvenile animal studies, and proposed clinical studies. This dialogue will be based on available evidence and help inform the most appropriate paediatric development strategy for the PIP. We propose the use of existing EMA procedures (SA, including parallel SA with FDA or with HTA bodies) on specific questions related to adult and paediatric development strategies, to provide a higher probability of success to achieve a program that meets the expectations of several regulators.

Secondly, the optimal timepoint for PIP submission in relation to the adult program can be established based on the data generation strategy discussed, potential program timelines and anticipated development milestones. Early discussions will allow appropriate buy-in and justification for the submission timepoint according to Article 16 of the Paediatric Regulation, while considering other ongoing activities of the overall program. It could also help tailor timelines to avoid multiple ongoing clinical trials competing for the same patient population with the risk of significant delay to completing those programs. Thorough preparation for the subsequent PIP procedure will ultimately speed up the PIP decision and reduce the need for subsequent modification procedures. Hence, it can help to address the steadily rising numbers of PIP modification procedures and save valuable regulatory resources.


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3. Component 2: optimised PIP procedures[5]

The integrated paediatric development dialogue will have provided regulators' advice, insights and recommendations related to the optimal design of the PIP and appropriate timing of its submission. This will subsequently facilitate a streamlined regulatory procedure to reach a binding PIP decision according to the Paediatric Regulation.

Once the developer submits the PIP to EMA for regulatory assessment, it will include all required aspects of the PIP based, as much as possible, on data rather than assumptions. This should speed up the decision on the "key binding elements" (KBE). As most aspects will have already been discussed during the design phase of the program, we expect that the EMA validation period could be significantly shortened and that the PIP could be assessed and agreed by PDCO within the standard 60-day timetable, i.e. without the need for a request for modification for the initial PIP.

If needed, the same approach could also be used during modification procedures. Significant program strategy modifications could be pre-discussed to clarify and explain more complex changes.

During the clock-stop, a resolution of the issues should be found to ensure that the 30-day period following the re-start of the clock can be used by PDCO to prepare the KBEs for the PIP decision. The applicant should work closely with EMA staff before formal adoption by the PDCO to ensure clear and accurate measures in the decision.

4. Expected benefit

The proposed model has significant benefits, including:

- Filing PIPs based on the best possible scientific evidence, which contain feasible trials that deliver new paediatric medicines in a timely manner, including children in trials only when truly needed. PIPs based on data with reduced reliance on assumptions will more likely lead to studies that complete within the agreed timelines and reduce the need for deferrals.
- Fostering an environment that encourages innovation. Allowing time to develop PIPs with the best scientific knowledge encourages and allows companies to design the best possible trials.
- The ability to identify appropriate paediatric unmet needs with input from a larger community, including parents, clinicians and paediatric networks, avoiding crowding in areas where needs have been met.
- Better coordination among the many actors in paediatric development, including regulators and their committees, with a more consistent understanding across key stakeholders of what is needed.

[5] Please note, detailed proposals for Component 2 will be captured in a separate paper [in preparation].


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- The duration of the PIP procedure could be significantly reduced, because PIP procedures should be finalised faster and more predictably. This will also contribute to less complex regulatory milestone-sequencing planning for Industry.
- In consequence, necessary resources for the PIP procedures could be better planned in both industry and regulatory agencies, because they are based on pre-agreed PIP submission timelines
- Attrition: the highest level of attrition is seen with more innovative medicinal products, which are often first-in-class or first-in-disease. As these will not have a PIP until enough data has been gathered to show the project is viable, this will save industry and health authority resources, that are normally invested in the PIP process. These resources could be re-focused instead on more value-added integrated development discussion activities.

In conclusion, our optimised regulatory interaction model will support the Paediatric Regulation to better deliver on its aim of facilitating the development and availability of medicines for children, due to faster agreement, implementation and execution of binding PIPs, which are based on robust scientific evidence, and operationally feasible clinical programs.


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