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Human Medicines Division

Review of the stepwise paediatric investigation plan (sPIP) pilot: Outcomes and future perspectives

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Abstract

The stepwise paediatric investigation plan (sPIP) pilot was launched to manage exceptional paediatric development programmes in which critical data are unavailable at the time of initial PIP submission, thereby constraining evidence-based planning of key study elements. Intended only for rare or complex developments with major scientific uncertainty, the sPIP allows for progressive definition of key elements through milestones agreed in advance with regulators. Between 2023 and 2025, 27 eligibility requests were received and eight sPIPs adopted, mainly in rare diseases and oncology. The pilot demonstrated feasibility and value supporting timely paediatric development while ensuring scientific rigour and flexibility for future integration into routine regulatory practice. Future efforts will focus on refining milestone management, embedding the framework into standard regulatory practice, and ensuring long-term monitoring of paediatric development programmes implemented under sPIPs, in order to safeguard sustained regulatory oversight and public health outcomes.

1. Introduction

Paediatric medicine development is a complex and tightly regulated process. The regulatory evaluation of medicines for children is particularly stringent to ensure robust evidence of their safety, efficacy, and appropriate formulation and dosing across relevant paediatric age-subsets.

When designing clinical trials to generate the data to support regulatory submissions, developers of paediatric medicines face unique challenges beyond those encountered in adult medicine development. Important challenges include heightened ethical considerations, age-dependant physiological differences, and, in most cases, limited patient populations available for inclusion in clinical trials.

Medicine developers are legally required under EU pharmaceutical legislation to submit a paediatric investigation plan (PIP) to the European Medicines Agency (EMA) at an early stage of product development. Such a plan must be submitted before completion of human pharmacokinetic/ pharmacodynamic studies in adults or before initiating studies in children in medicines only intended for paediatric use. The PIP is not just a collection of study protocols, rather it should present a research and development programme in an overarching plan designed to generate sufficient, high-quality data to support the authorisation of a medicinal product in the paediatric population. The PIP thus ensures that medicines intended for paediatric use are of appropriate quality, undergo adequate clinical evaluation, and generate robust data supporting their safe and effective use in children by integrating paediatric development early in the overall programme.

Upon submission by the developer, the PIP is assessed by EMA with its Paediatric Committee (PDCO), leading to an EMA decision within the timelines set out in the Paediatric Regulation[1]. Because medicinal product development is inherently dynamic and data-driven, and because a PIP is by nature a prospective planning instrument submitted before full evidence generation, a degree of scientific uncertainty is both inevitable and expected at the time of initial PIP assessment. This often necessitates later modifications to reflect scientific advances, new evidence, or to address implementation difficulties. Although a PIP may be modified, after PDCO agreement in response to a formal request, if evidence shows that the initial plan may be inappropriate or difficult to implement, the regulatory framework requires that all measures in the initial PIP application are agreed upon in the form of "key elements": critical components of the development plan that must be fulfilled. These

[1] EMA website, Paediatric Regulation, https://www.ema.europa.eu/en/human-regulatory-overview/paediatric-medicines-overview/paediatric-regulation

key elements cover non-clinical, quality and clinical aspects, as well as considerations on modelling and simulation, and extrapolation.

However, in exceptional cases notably for innovative treatments and developments in rare diseases, critical data for establishing these key elements may not be available early in development, beyond the uncertainty normally expected from a forward-looking development plan. Such data gaps may lead to uncertainties related to optimal dosing, the identification of suitable paediatric study populations, or rapidly evolving scientific knowledge.

To address these challenges, EMA explored the **stepwise paediatric investigation plan (sPIP) concept**. The sPIP is based on a structured, milestone-driven process that enables progressive refinement of key elements as more data become available while maintaining regulatory oversight. Rather than requiring a fully defined plan at the outset, an sPIP submission provides a preliminary but comprehensive framework outlining the condition to be treated, targeted paediatric subpopulations, initial study concepts, and projected completion timelines. All evidence available at submission must be provided and considered, and the sPIP should define as many key elements as possible, even if initially at a less detailed level, or as a concept in order to develop the plan. Critical parameters that cannot yet be determined are formally revisited and agreed at predefined milestones within the stepwise process.

Following extensive consultation of stakeholders on the concept, the sPIP pilot was started in the first quarter of 2023. Applicants were able to request inclusion in the pilot either through the AskEMA platform[2] or by contacting EMA scientific officers directly.

A review was planned once eight initial sPIP opinions had been adopted with the objective of gathering experience, refining the framework and informing decisions on its potential integration into routine regulatory practice. This report presents the key operational and procedural features of the sPIP framework and assesses its effectiveness and efficiency at the stage of initial opinion, from a regulatory and policy perspective.

2. Methods

The review focused on key operational and procedural aspects of the sPIP framework to assess its effectiveness and efficiency.

2.1. Data collection

- Information was compiled on the number and nature of eligibility requests and submitted sPIPs, pre-submission meeting statistics, timelines from eligibility request to PIP opinion, and therapeutic areas covered.
- Data were gathered from multiple sources, including the AskEMA platform, direct communications with EMA scientific officers, PDCO plenary discussions, and internal databases.

2.2. Analysis of eligibility requests and submissions

- The number and outcomes of eligibility requests and sPIPs submitted for assessment were recorded (e.g. acceptance or rejection).
- The therapeutic areas were categorised to identify trends and areas of high demand.

[2] EMA website: https://www.ema.europa.eu/en/about-us/contacts-european-medicines-agency/send-question-european-medicines-agency

2.3. Timelines analysis

- The frequency and timing of pre-submission meetings were analysed.
- Time intervals were calculated between eligibility request, pre-submission meeting, sPIP submission, and PDCO opinion.

2.4. Types of medicines included

- Medicines were categorised as chemical, biologic, or advanced-therapy medicinal products (ATMPs).

2.5. Quality, non-clinical, and clinical study considerations

- The inclusion of quality, non-clinical and clinical studies in the agreed sPIPs was recorded.
- Key elements pending definition at submission were identified and analysed.

2.6. Waivers

- The presence or absence of waivers in the agreed sPIPs at submission was documented.

These analyses were used to characterise the operational performance of the pilot and to identify trends across therapeutic areas, product types, and procedural timelines.

3. Results

3.1. Overview of submissions

The pilot started in February 2023; PDCO adopted its eighth opinion of an sPIP in January 2025. During that period, a total of 27 eligibility requests were received. Most requests (25) came through the AskEMA platform, one was made directly to an EMA scientific officer, and another originated from a discussion during a PDCO plenary meeting.

Of these, 15 stepwise PIPs were subsequently submitted for assessment via the standard EMA submission process. The PDCO determined that one application was unsuitable for the stepwise framework. At the time of this review, eight sPIP opinions had been adopted.

Applications were not accepted into the pilot when (i) a PIP was already ongoing or agreed for the same active substance, (ii) pre-submission meetings or PDCO discussions demonstrated that a conventional PIP could be defined without a stepwise approach, or (iii) multiple requests were received in the same therapeutic area, as the pilot was limited to eight opinions and aimed to gather experience across a broad range of therapeutic areas.

3.2. Procedural timelines

Ten pre-submission meetings were held during the pilot period as some requests resulted in submission without such a meeting. The time from eligibility request to pre-submission meeting ranged from five days to six months (median: 1.5 months), reflecting scheduling challenges in some cases where it was difficult to align availability across all participants. The interval between pre-submission meeting and PIP submission varied from 1.5 to five months, while PIP submission to opinion took between ten and fourteen months. Estimated completion of the associated paediatric development programmes is projected between 2029 and 2035.

3.3. Therapeutic areas

Eligibility requests most frequently covered medicinal products intended to treat neurologic and metabolic genetic disorders (n=9) and oncology medicines (n=7). Other requests covered medicines in the area of immunology (n=3) and cardiology (n=2). One request was received for medicines in each of these areas: respiratory diseases, neurology, nephrology, hepatology, psychiatry, and endocrinology (see figure below).

At the time of review, PDCO had adopted 8 opinions for products in neurologic and metabolic genetic disorders (n=4), immunology (n=2), hepatology (n=1) and oncology (n=1).

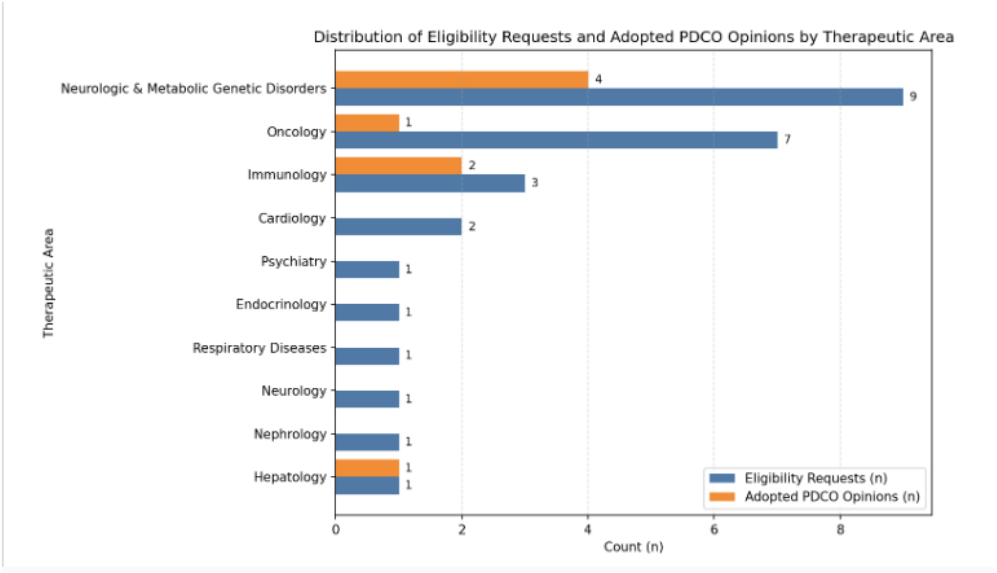

Figure 1: Distribution of sPIP eligibility requests by therapeutic area.

There was approximately equal distribution between chemical and biologic, or advanced-therapy medicinal products (Fig. 2)

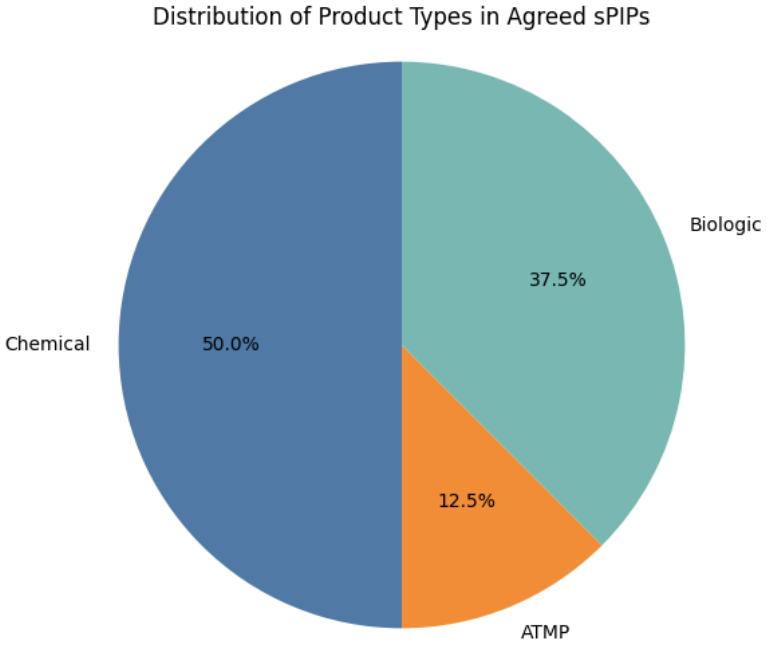

Figure 2: Product types for the agreed sPIPs.

3.4. Type of studies

The eight sPIPs with an adopted opinion were examined in greater detail to analyse both the types of study included and whether certain key elements were more frequently left undefined at the stage of the initial submission.

Quality studies outlining requirements to develop age-appropriate formulations were incorporated into six of eight agreed sPIPs. Non-clinical studies were included in five of the eight agreed sPIPs. One non-clinical study in an sPIP for an oncology medicine was identified as critical for a go/no-go decision.

In total, these sPIPs included 21 clinical studies, with each sPIP containing between two and four studies.

The most commonly undefined key elements in these initial sPIPs were sample size and dosage, with sample size not defined in 12 out of 21 studies and dosage not defined in 10 out of 21 studies (figure 3). Other undefined elements included endpoints (not defined in eight studies), duration of study (not defined in five studies), statistical analysis (not defined in six studies), and control (not defined in two studies).

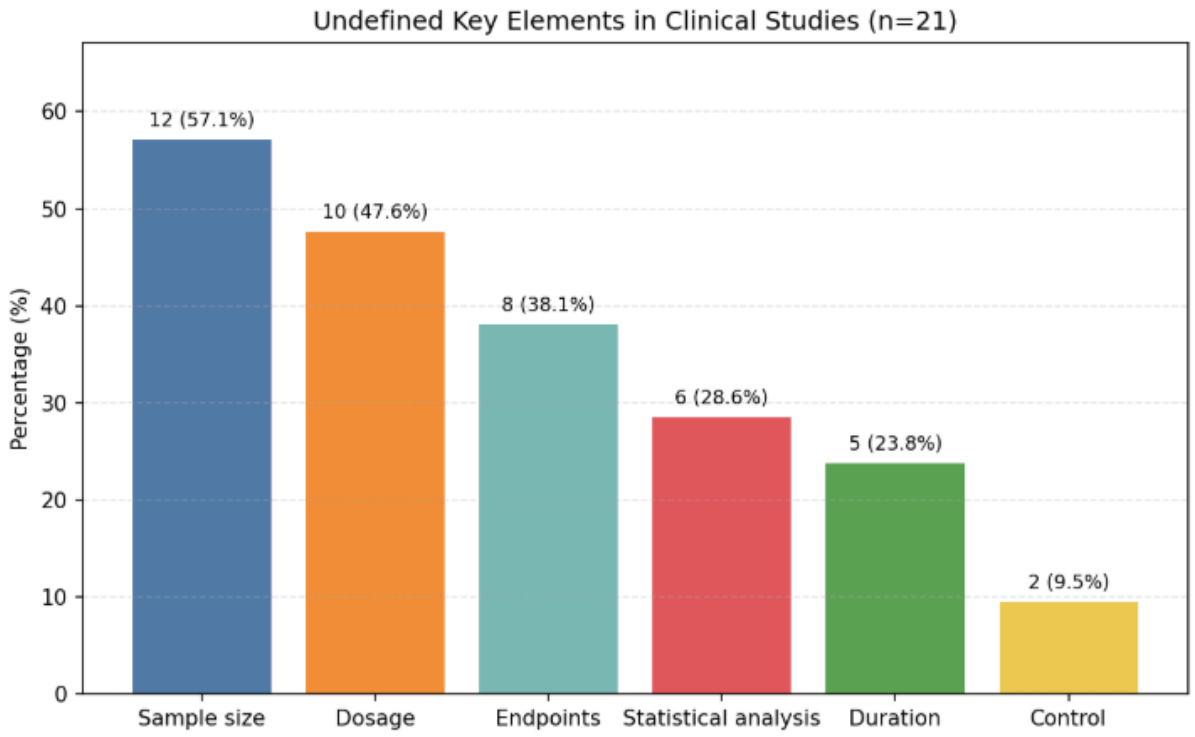

Figure 3: Distribution of undefined key elements in clinical studies included in the sPIPs.

3.5. Waivers

No waivers were granted in five of the eight agreed sPIPs, which contrasts with the usual practice where most PIPs include a partial waiver. This reflects the predominantly paediatric focus of these programmes, as they addressed diseases that primarily affect children, such as genetic conditions presenting from birth, making partial waivers inappropriate in more than half of the cases evaluated.

4. Discussion

From the start of the pilot to the time of analysis, 27 eligibility requests were received; these were reviewed for inclusion in the pilot based on pre-defined selection criteria. The pilot was completed following PDCO adoption of eight sPIP proposals. A detailed review of these eight adopted sPIPs revealed that the specific nature of these complex developments led to knowledge gaps normally needed for initial agreement of a robust paediatric development plan. As a result, key study parameters such as sample size, dosage, endpoints, statistical analysis, and duration, which are essential for assessing feasibility and scientific validity, could not be provided. These findings highlight the complexity of developing paediatric plans for such innovative treatments that were included in the pilot hence requiring early, structured dialogue to eventually ensure completeness and regulatory compliance.

4.1. Advantages of the stepwise approach

The sPIP framework accommodates the iterative nature of paediatric medicines development, in which early evidence progressively informs subsequent study design. This flexibility may prevent unnecessary delays in study initiation by enabling early interaction between developers and regulators, particularly crucial for medicines addressing life-threatening or rare paediatric conditions.

The milestone-driven process also fosters closer interaction between pharmaceutical developers and regulatory authorities. Regular assessments at predefined milestones facilitate timely feedback, dialogue, and course corrections, supporting alignment with evolving scientific evidence and regulatory expectations. In addition, this approach is expected to encourage developers to engage earlier and maintain ongoing discussions as their programmes progress, thereby promoting continuous collaboration and proactive planning throughout the development lifecycle.

4.2. Regulatory efficiency and applicability

The results indicate that the sPIP approach provides a structured mechanism for addressing data gaps in situations where critical elements cannot be defined at initial submission. This is demonstrated by the finding that all eight adopted sPIPs contained missing key elements, such as sample size, dosage, and endpoints, at the time of initial submission. These gaps will progressively be addressed through milestone-driven interactions, showing that the stepwise approach enables developers to refine and complete paediatric development plans as new evidence emerges. This approach is particularly relevant in cases where significant knowledge gaps exist and additional information from early studies is needed before a complete PIP can be agreed upon.

This framework has more utility in rare paediatric diseases and oncology, where uncertainty and limited prior evidence are common. The more frequent absence of waivers in sPIPs compared with standard PIPs reflects the predominantly paediatric nature of the diseases under evaluation. In many cases, these conditions, such as genetic disorders presenting from birth or early childhood, affect the paediatric population almost exclusively, leaving little or no scientific justification for granting waivers. This pattern suggests that the sPIP framework is particularly suited to programmes targeting unmet paediatric medical needs in rare diseases.

The time from PIP submission to agreement was similar to that of conventional PIPs, at around 12 months. This suggests that the clock-stop period remains a significant factor in the overall timeline.

4.3. Limitations and future monitoring

A structured milestone-driven approach is necessary: clear timelines should ensure that paediatric development remains a priority and a structured approach ensures that the PIP remains a plan and does not contain the detailed protocols for each measure. However, the current review only captures the initial PIP opinion and does not cover the entire lifecycle of the development plans. Long-term monitoring will be required to determine whether milestone-driven updates support timely and efficient completion of paediatric studies and subsequent authorisation. This monitoring will also need to be extended to future sPIPs if this process is to be integrated into regulatory practice.

The stepwise approach introduces additional procedural challenges. The modification process remains bound by the 60-day timeline without any clock-stop provision, making it difficult to accommodate the complex revisions anticipated under the sPIP framework. Pre-submission meetings will continue to play a critical role in planning these modifications and may become more frequent, potentially increasing the overall burden on the system.

Further analysis will be required to evaluate applicants' adherence to the conditions outlined in the initial PIP opinions, ensure appropriate modifications to the PIP, and assess the impact of milestone management on overall development timelines.

Evaluation of the entire lifecycle is a long-term project; as most ongoing sPIPs are scheduled for completion between 2029 and 2035, systematic follow-up will be essential to evaluate their long-term regulatory and clinical outcomes.

5. Next Steps

Transitioning from the pilot phase to an established procedure will require targeted actions to consolidate experience gained and ensure sustainable implementation within the paediatric regulatory framework. This involves several key actions:

5.1. Transition to an established procedure

- Conclude the pilot phase and integrate the sPIP framework into the existing paediatric regulatory landscape on a voluntary basis.
- Develop and publish updated guidance documents on the EMA website.
- Maintain the principle that the sPIP is a **complementary mechanism** intended for exceptional cases, not a general alternative to standard PIPs.

5.2. Continued engagement with stakeholders

- Foster dialogue with developers, researchers, patients and other stakeholders to ensure alignment of the framework with regulatory and scientific expectations.

5.3. Addressing complex sPIP modification procedures

- Recognise that future modification procedures may be more complex and require detailed discussions under the stepwise approach due to iterative updates within fixed timelines.
- Plan for pre-submission meetings to ensure that modifications are adequately justified and supported by scientific evidence.

5.4. Continued monitoring and evaluation

- Establish a monitoring system to follow the progress of ongoing sPIP procedures, focusing on key performance indicators such as:
  - submission timelines and opinion adoption;
  - compliance with agreed milestones and initial PIP conditions;
  - number and nature of modification procedures;
  - timing of paediatric indication approvals relative to adult indications.
- Commit to long-term evaluation of the framework, recognising that most sPIPs in the pilot are expected to complete between 2029 and 2035.
- Use these data to assess whether the sPIP approach facilitates timely, evidence-based paediatric development and supports public-health objectives.

6. Conclusion

The sPIP pilot has demonstrated both feasibility and utility in regulatory practice, offering a structured and flexible approach to support paediatric drug development. While fully defined PIPs at initial submission remain the primary route with the necessary evidence present in most cases, the stepwise approach provides a valuable alternative for exceptional complex cases where critical data are lacking at the time of initial submission. The need for such an approach has been recognised also in the proposed revision of the pharmaceutical legislation.

The pilot confirmed that the stepwise framework supports early engagement between developers and EMA/PDCO and has been well received. Pre-submission meetings as well as available published guidance have proven instrumental in guiding applicants, ensuring well-prepared submissions aligned with regulatory expectations.

Most requests for sPIPs were in rare genetic diseases and oncology. The ability to refine key elements after initial submission enables the development of more scientifically robust PIPs. This flexibility avoids reliance on unfounded assumptions when critical information, such as sample size, dosing, or endpoints, is not available at the outset. Instead, plans can evolve as early studies generate evidence, allowing study designs to be based on real data rather than speculation. The frequency of missing key elements observed in the pilot underscores the need for such flexibility, as it reflects the reality that essential details often emerge only as development progresses. This iterative approach enhances the quality and feasibility of paediatric clinical trials and demonstrates the framework's suitability for complex, data-limited settings.

Future priorities include optimising milestone management and ensuring timely data availability to minimise delays. The clock-stop period for addressing PDCO questions remains a significant factor in the overall timeline, indicating that further refinements may be necessary. Systematic long-term monitoring will assess whether this flexible approach helps accelerate the development and availability of medicines for rare paediatric diseases, ensuring that children with the greatest unmet medical needs can access treatments sooner.