EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The Stepwise Paediatric Investigation Plan (sPIP)

11th Industry stakeholder platform on research and development support

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General principles of the stepwise PIP (sPIP)

- In general, it is expected that all **PIP measures** can be agreed upon at the time of the **initial PIP application**

- For the rare cases when **crucial data are not yet available** to sufficiently define the key elements (KEs) of the planned measure at the time of the initial PIP application → **stepwise PIP approach** → **Opinion on a plan not yet fully defined**

- **KEs that cannot be defined → data required for defining them and by when**

- **Minimum set of data** (condition, age subsets, preliminary outline of planned studies and completion date) required

- The sPIP will be modified when relevant data available → **fully developed PIP at the end** (same details as for conventional PIP)

- **Paediatric development should not be delayed**

When could it be appropriate to apply for a sPIP?

- **Case by case decision** (stage of development, data available on product, knowledge of disease *et cetera*)
- If **precedence or regulatory guidelines exist**, it is not expected that a stepwise PIP approach is needed
- **Scientific justification** always required on the KEs that cannot be determined
- Wide **scope**: from "*only a few KEs cannot be defined*" to "*Most KEs of certain studies cannot be defined*"

Practical aspects

• Applicants advised to **contact the EMA Paediatric medicines (PME) office via AskEMA** to explore the potential of this approach and the need for a **pre-submission meeting**

• If a procedure is eligible for the stepwise PIP approach will be determined at **validation stage and confirmed (or not) by the PDCO at the D30 discussion**

• If the approach is **not considered sufficiently scientifically justified**, applicant is invited to submit a **conventional PIP**

• For the submission the **same template** as for conventional PIP should be used (advice on practical aspects included in guidance document)

When applying for a sPIP

- It should be clear from the submission **which data will be needed to fully define a KE and how and when the missing data will be generated**
- **Timelines** should be linked to milestones → reflected in the Opinion
- PIP Opinion will be updated via **subsequent modification procedures at the times specified**
- In case of significant modifications a **pre-submission meeting** with the assessment team is recommended
- **Compliance check** remains unchanged

Possible Key Elements in initial sPIP Opinion

Study identifier(s)	Not yet available
Study design features and main objectives	Clinical trial to evaluate pharmacokinetics, safety and tolerability of <NAME> in children from 2 years to less than 12 years of age with <CONDITION>. The exact design features, including study design, controls and justification for extrapolation of efficacy and elements to be included in the PIP opinion must be based on results from Study 2 and agreed with the PDCO after Study 2 primary analysis at 24 weeks.
Study population and subset definition	Male and female paediatric patients from 2 years to less than 12 years of age with <CONDITION>.
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	The number of subjects evaluable for the primary pharmacokinetic (PK) analysis and the minimum number of patients with body weight inferior to 40kg must be based on results from Study 2 and a modification must be agreed with the PDCO after Study 2 primary analysis at 24 weeks to determine the number of study participants.
Study duration for participants	• Treatment duration: must be planned for at least 52 weeks in protocol.

Statistical plan including study conduct and analysis	To be determined. This element must be agreed by the PDCO as specified above. The plan should make clear when the study will be considered positive.
Other	Not applicable
Plan for specific follow-up (not part of completion of this study)	To be discussed and agreed with the PDCO before submission of the regulatory application for <CONDITION> in adults and adolescents.
External data safety monitoring Board	Required.
Date of initiation	To be discussed and agreed with the PDCO no later than 4 months after Study 2 primary analysis at 24 weeks and before submission of the regulatory application for <CONDITION> in adults and adolescents. The initiation of this study is deferred.
Date of completion (last patient, last visit)	By June 2028. The completion of this study is deferred.

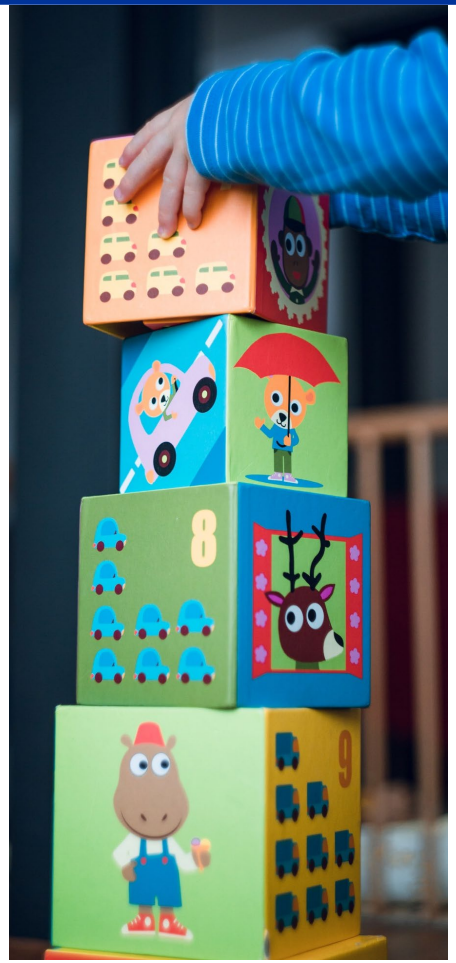
EMA launched sPIP pilot in early 2023

Initial contact through askEMA

Allocation to PME officer with expertise in the area

If needed PDCO member with expertise in the area invited

Teleconference to discuss suitability



sPIP pilot

Requests

16 expr. of interest

7 qualify
7 under discussion
2 rejected

5 sPIPs applications submitted

Steps

- PDCO decides on D30 if application appropriate for sPIP pilot
- Advice provided during pre-submission meeting on suitability for sPIP pilot

Reasons for potential rejection

- Ongoing PIP
- Previous PIP for the same active
- After the pre-submission meeting it became clear how the development programme could be defined

EMA aims to analyse pilot results when 8 sPIP Opinions adopted, expected Q4 2024

Oncology

Metabolic diseases

Cardiology

Neurology

Respiratory diseases

Immunology

Reasons for applying

- Data on **activity against paediatric cancers** need to be generated
- Challenges with development in **ultra-rare conditions** for **dose finding** and **endpoints**
- **Lack of relevant animal model**, no established PD markers or endpoints
- **Study in infants first** (most affected), then in older children and adolescents
- Collection of **natural history data** first, before defining the PIP
- **Condition in children different to adults**, no proof of concept in humans yet
- Rare, **life-threatening disease, recently identified in children**, no approved medicine no regulatory guidance and no validated endpoints

Further information

sPIP guidance

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-stepwise-pip-pilot_en.pdf

Enquiries on whether your application qualifies for a sPIP

Ask the EMA at:

https://www.ema.europa.eu/en/about-us/contacts/send-question-european-medicines-agency

Next steps

-continue to monitor progress of pilot

-review of experience once 8 sPIP opinions are adopted

-estimated in Q4 of 2024

-in parallel, review experience from new scientific document and KEF

-update guidance and documents as necessary