EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Closing report from the Focus group on the practical application of principles relevant for the PIP framework

9th Industry Stakeholder Platform on Research and Development support

05 December 2022

Presented by Chrissi Pallidis (EMA) and Sabine Scherer (BfArM) together with Gesine Bejeuhr (EFPIA) and Marcello Milano (EUCOPE)

# **Where we started in 2021:**
## Focus group meetings and participants

Constitution of the Focus group agreed at the 5th Industry stakeholder platform on research and development support in November 2020: [5th Industry Stakeholder Platform on R&D support 16.11.20 - highlight report (europa.eu)]

- 8 Video Conferences (April – November 2021)
- Participants
  - Industry representatives from trade associations
  - Vice-Chair PDCO, EMA representatives

# Objective and expected outcomes

**To explore a PIP model that allows, in certain cases, the paediatric development programme to become more defined over time as more evidence becomes available. The group should discuss possibilities for and limitations of such PIP model that allows to develop along with the evolution of scientific knowledge.** ✓

- Reflections on a scientifically sound basis and in compliance with the regulatory requirements
- Consideration should be complemented with illustrative examples.

| | |
|---|---|
| **Criteria** for the identification of paediatric developments that would qualify for a step-wise approach to agree the binding elements in the PIP | ✓ |
| **Concepts** for planning milestones on the basis of available evidence, with resulting binding elements and commitment for future interaction | ✓ |
| **Analysis of risks** inherent of such model(s), including potential delays of paediatric development, as well as resource investment | ✓ |
| **Outline of a supporting framework** for dialogue in context of such PIP submissions | ✓ |

In addition discussion about key elements form in general for all PIPs

# Key Elements – Clinical – Perspective and Proposals

**High-level**

- Study identifier
- Type of study
- Design
- Type of control
- Objective
- Randomisation
- Blinding
- Minimum number of paediatric participants

**Details**

- Study design features and main objectives
- Study population and subset definition
- Number of study participants by paediatric subset
- Study duration for participants
- Dosage, treatment regimen, route of administration
- Control(s) – Duplicative with other high-level sections
- Primary endpoint(s) with time point(s) of assessment
- Main secondary endpoint(s) with time(s) of assessment (Optional) – The primary endpoint is usually the main determinant for success
- Statistical plan including study conduct and analysis – A lot of detail not needed for key elements. Key are the endpoints and results.
- Other – If it does not fall under categories, likely not of value
- Plan for specific follow-up (not part of completion of this study) – This is captured as part of a CTA approval or in the RMP for when the paediatric indication is approved.
- External Data safety monitoring Board (yes / no) – Level of detail not considered needed and as process would be done if needed as part of a trial.

**Timelines and dependencies**

- Date of initiation - Captured in deferral report and completion is the key timeline.
  - Additional dependencies
  - Deferral for initiation requested – Yes/no –
- Date of completion – Having this field even for high-level PIP to capture if the plan is before or after MAA – ensure studies are done as early as possible.
  - Additional dependencies
  - Deferral for completion requested – Yes/no

**Key**

Most important key features

Further detail elements covered in scientific PIP doc

Least important / duplicative / unnecessary- suggest removing

**Justification points added for select items**

# **In 2022:** Focus group meetings and participants

- Focus group on the practical application of principles relevant for the PIP framework agreed at the 7th Industry stakeholder platform in November 2021:
- 7 Video Conferences (March – Oct 2022)
- Participants:
  - Chrissi Pallidis, Giovanni Lesa, Gunter Egger, Ralph Bax, Marie-Helene Pinheiro, Michael Berntgen (EMA),
  - Sabine Scherer + other PDCO members ad hoc (PDCO),
  - Andrea Braun-Scherhag, Bertrand Fournier, Marcello Milano (EUCOPE); Angelika Joos, Geneviève Le Visage (until May), Pauline Roudot (May onwards), Gesine Bejeuhr, Mireille Costantzer (EFPIA); Emi Aydin, Laura Liebers, Richard Vart (EuropaBio); Karen Jourdan- Brown (Vaccines Europe)

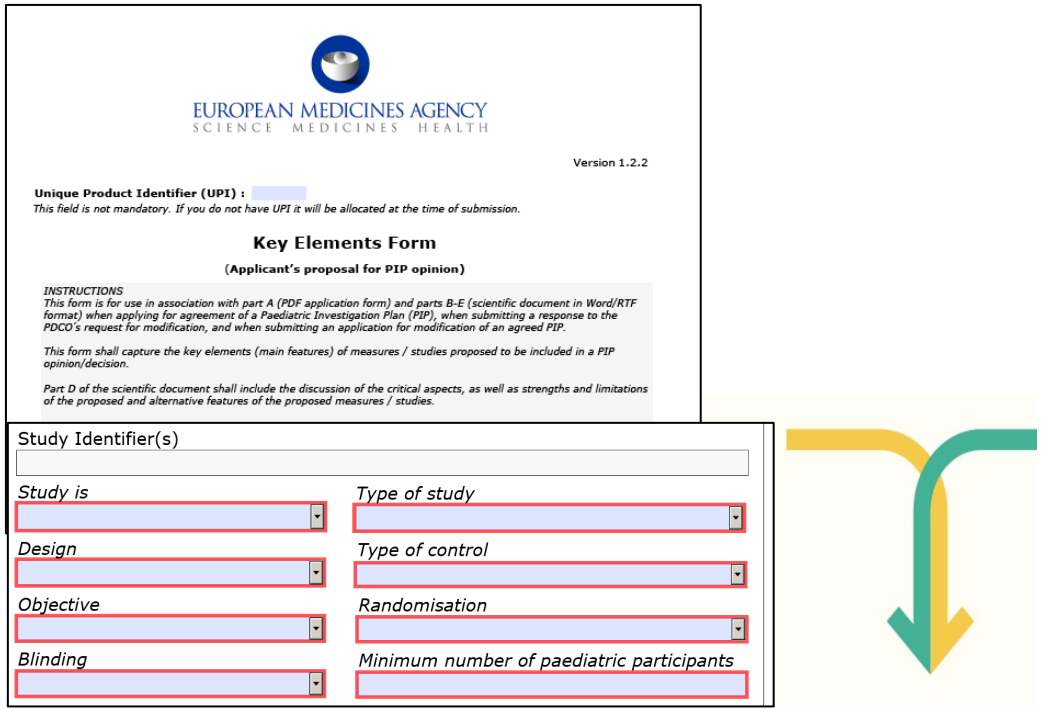
# Objective and expected outcomes

The objective of this group is to develop further the principles that were established in the Focus group on the concept of an 'evolutionary' PIP in order to guide the practical application. The primary focus is on the 'evolutionary' PIP to support the preparation for piloting and testing of the concept. Furthermore, the initial discussion on key elements for a PIP in general should be matured to support a review of the applicable guidance. The following outcome is expected:

- **Concise description of the 'evolutionary' PIP model** including elements to guide a scientific justification to support a case-by-case discussion on the application of the concept;
- **Outline of practical arrangements and pathways that support integrated dialogue** on an 'evolutionary' PIP, including multi-stakeholder dialogue as required;
- **Comprehensive review and identification of suitable key elements for a PIP** ('evolutionary' and regular), to describe and agree a paediatric development programme robustly from a scientific and regulatory perspective;
- **Development of milestone terminology for PIPs** that ensures clarity of activities and dependencies and reduces unnecessary modifications.

Please note, this concept is now called **stepwise PIP**

# Key Element Form and Opinion template



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Version 1.2.2

**Unique Product Identifier (UPI) :**
*This field is not mandatory. If you do not have UPI it will be allocated at the time of submission.*

**Key Elements Form**

**(Applicant's proposal for PIP opinion)**

*INSTRUCTIONS*
*This form is for use in association with part A (PDF application form) and parts B-E (scientific document in Word/RTF format) when applying for agreement of a Paediatric Investigation Plan (PIP), when submitting a response to the PDCO's request for modification, and when submitting an application for modification of an agreed PIP.*

*This form shall capture the key elements (main features) of measures / studies proposed to be included in a PIP opinion/decision.*

*Part D of the scientific document shall include the discussion of the critical aspects, as well as strengths and limitations of the proposed and alternative features of the proposed measures / studies.*

Study Identifier(s)

*Study is* | *Type of study*

*Design* | *Type of control*

*Objective* | *Randomisation*

*Blinding* | *Minimum number of paediatric participants*

Opinion template:

| | |
|---|---|
| **Study design features and main objectives**<br>*Study design and main objectives fields have been combined. If you have generated the Annex I from the database, you would need to manually combine these 2 fields.* | *Copy and paste into the <Text> field the study description from the summary table. Additionally, select from the below objectives, and add others if relevant.*<br><br><Text> in terms of <superiority of X over placebo/control>, <reduction of Y> <non-inferiority of X as compared to Y with respect to Z> and <to provide <PK/PD data to support the extrapolation of efficacy from other populations> <to contribute to modelling of the PK/PD/exposure /dose-response relationship> in children from age to age <(and adults)> with <broad population definition>, <with extension study to evaluate safety>. |
| **Study population and subset definition**<br>*Eligibility fields have been deleted (inclusion and exclusion criteria). If you have generated the Annex I from the database, you would need to manually combine delete the rows and details any required specifics for eligibility criteria in this field.* | *Include gender, age range and condition, e.g.:*<br><br>"Male and female children and adolescents 6 to less than 18 years of age with condition X."<br><br>*Specify **main** and **relevant** eligibility criteria here if necessary (e.g.,* diagnosis of glaucoma and IOP > 21 mmHg*).*<br><br>*For those studies mixing paediatric and adults, mention it in brackets e.g.,* "(and in adults)". |

**Agreement to merge them in one single document**

# Remaining open tasks after July 2022

| | |
|---|---|
| **Key elements**<br>• Finalisation of Merged Opinion / Key element Form | ✓ |
| • Implementation of updated opinion form with revised key elements early 2023 | ✓ |
| **Stepwise PIP**<br>• Pre-pilot to help with drafting the guideline and try out how the stepwise PIP can work in practice. | ✓ |
| • The pre-pilot would use the usual PIP application and evaluation framework. Call for candidates in the pipeline for pre-pilot. | ✓ |
| • Stepwise PIP-pilot start end of 2022 | ✓ |

# Guidance document on stepwise PIP/Pilot 2022/23

**General principles:**

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

- There may be certain cases where **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 partly developed plan**

- **Minimum set of data** (condition, age subsets, completion date) required

- **Subsequent PIP modifications** to complement the plan -> **fully developed PIP** (same as for conventional approach)

- **Paediatric development should not be delayed**

# Guidance document on stepwise PIP/Pilot

**When could it be appropriate to apply for a 'stepwise' PIP?**

- **Case by case decision** (examples provided in the guidance document)
- **Scientific justification** which study /KE can or cannot be determined required
- If **precedence or regulatory guidelines** exist, it is not expected that a stepwise PIP approach is needed
- Wide **scope:** *"only a few KEs cannot be defined"* to *"whole studies cannot be defined"*

# Guidance document on stepwise PIP/Pilot

**Procedure:**

- Applicants are advised to **contact the EMA Paediatric office (PME) office** to explore the potential of this approach and the need for a **pre-submission meeting**
- If a procedure is eligible for the evolutionary PIP approach will be determined at **validation stage or following the PDCO D30 discussion** the latest
- 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)

# Guidance document on stepwise PIP/Pilot

**Procedure:**

- It should be clear form the submission **which data will be needed to 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**
- In case of significant modifications **a pre-submission meeting with the assessment team** is recommended
- **Compliance check** remains unchanged

# Key elements form

Main principles:

- Update of the format to resemble agreed opinion
- Removal of repetition
- Removal of unnecessary detail
- Possibility to update contingent measures as data are generated via modifications

# From protocol details…

| | |
|---|---|
| Primary endpoint(s) with time point(s) of assessment | <Text><br><Change in measure A between time point X and time point Y.><br><Proportion of patients with outcome B at time point X> <as compared to placebo/comparator.><br><Relapse-/Disease-/Progression-/Event-free / overall survival rate at time X> <as compared to placebo/comparator.><br><Relapse-/Disease-/Progression-/Event-free / overall survival probability> <as compared to placebo/comparator.><br><Pharmacokinetic parameters including, e.g., Cmax, AUC, t1/2, Csteadystate, Ctrough> <using <number> samples per participant> <using sparse sampling.><br>*If relevant (e.g., PK in very young infants/neonates), provide specifics on PK sampling/blood volume strategy.* |
| Main secondary endpoint(s) with time(s) of assessment | **ONLY IF RELEVANT OR ONLY SECONDARY ENDPOINTS REQUIRED BY PDCO. LIMIT TO THE 2-3 MOST IMPORTANT SECONDARY ENDPOINTS. PK ENDPOINT FROM ABOVE MAY BE USED HERE.**<br>I. <Any endpoint in subset of patients with certain treatment duration.><br>II. Safety <and tolerability> assessments.<br>III. Acceptability <and palatability> assessments.<br>*In general, the acceptability and/or palatability of the paediatric formulation should be tested/confirmed in the clinical trial with the target population, not only in adults.* |

# …to study concepts

| | |
|---|---|
| Key evaluations and outcomes<br>*- major change-* | <Text> <<primary>, <secondary>endpoints> <key objectives and outcomes><br>*Bulleted list potentially with time point of assessment.*<br>*This section should include only the critical evaluations and outcomes important for establishing the paediatric indication. These are usually the primary endpoint but not necessarily limited to this. In cases where a primary endpoint cannot be defined it may be acceptable to include a primary objective here e.g. to collect efficacy information and further details on the primary endpoint to be added following a certain milestone (e.g. from a study in adults, or an earlier phase study in children). For small open label studies it may be appropriate to not define endpoints as primary or secondary as such studies are not powered for primary endpoint.*<br>*When **secondary endpoints** are required to be included in the opinion **only the most relevant** should be added here. This is not intended to be a copy from all endpoints included in the protocol but a summary of those considered most relevant. Occasionally exploratory endpoints are considered very important (e.g. important endpoints to advance the field on a specific issue).*<br><Pharmacokinetic parameters including, e.g., Cmax, AUC, t1/2, Csteadystate, Ctrough> <using <number> samples per participant> <using sparse sampling.> |

# Next steps

**Key elements**

- Implementation of updated opinion form with revised key elements early 2023

**Stepwise PIP**

- Publication of guidance and sPIP-pilot start end of 2022/beginning of 2023

- Convert Focus Group (regular meetings) into
  Sounding Board (meetings / feedback on as-need basis)

# Thank you

## Further information

Chrissi.Pallidis@ema.europa.eu

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Follow us on **@EMA_News**