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Guidance for stepwise PIPs (sPIPs)

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1. General principles of the stepwise PIP (sPIP)

By definition, a paediatric investigation plan (PIP) is a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population. In principle, the PIP shall be submitted not later than upon completion of the human pharmacokinetic studies in adults, or, particularly for paediatric-only developments, before any trials in children are started, i.e., early in the product development and therefore, as it is a plan, it may be subject to subsequent change as more evidence becomes available. The PIP is assessed by the Paediatric Committee (PDCO), and results in an EMA Decision within the timelines set out in Regulation (EC) No 1901/2006 (Paediatric Regulation).

As the development of medicinal products is a dynamic process dependent on the result of ongoing studies, some level of scientific uncertainty might be present at the time of the PDCO's initial assessment of the PIP, leading in most cases to the need to further modify the PIP where necessary (e.g. to align with scientific advances, new evidence generated and/or address difficulties with its implementation such as to render the PIP unworkable or no longer appropriate).

In general, it is expected that all measures needed to collect appropriate data for determining whether a paediatric indication for the target age-range may be authorised, shall be agreed upon at the time of the initial PIP application.

Nevertheless, there might be exceptional cases where crucial information needed to define relevant parts of the plan (e.g., whether a clinical study for a whole age group is necessary, and if so, the details of the study) are not yet available to sufficiently define the key elements of the planned measure at the time of the initial PIP application. In such rare cases, where uncertainties of such a level exist, agreeing on elements in PIP studies should be avoided. The concept of the 'stepwise PIP' (sPIP) was therefore born, consisting of only a partial development programme, conditional on the development of a full PIP once the crucial information has become available.

In any case, sPIPs must contain a minimum set of data (including condition, preliminary outline of planned studies based on available evidence and a PIP completion date) as a basis which should consider the state-of-the art scientific knowledge and current drug development experience in the relevant field. The sPIP would then be complemented through subsequent planned PIP modifications, based on the milestones/timelines for the submission of PIP modifications as agreed with the PDCO at the time of the initial PIP assessment and following the availability of new information/data or increased scientific knowledge. This approach would provide clear deadlines for the development of the full PIP and would avoid a high number of minor modifications submitted on an *ad-hoc* basis.

The modification of an sPIP follows the same procedure as the modification of any other agreed PIP. The goal is to have a full PIP as in the cases with 'conventional' (i.e., full) initial PIP applications. The full PIP would support collecting appropriate data to determine whether and under which conditions a medicinal product may be authorised for a paediatric indication.

2. Applying for a stepwise PIP

In cases where the sPIP approach is envisaged, a dedicated pre-submission meeting with the assessment team is strongly recommended.

In the presence of relevant existing guidance and precedence (including agreed PIPs in similar therapeutic areas) it is **not** expected that a stepwise PIP approach would be warranted in most cases.

2.1. When could it be appropriate to apply for an sPIP?

An sPIP submission should be considered based on the complete scientific context. For each element of the sPIP that cannot yet be defined, applicants should provide a scientific justification explaining why this is not yet considered feasible and describe any dependencies with other measures of the PIP.

Examples of cases that may justify a sPIP may include – but are not limited to – a first medicine for a disease (e.g., very rare disease only recently identified in children), a medicine whose mechanism of action has not been fully characterised yet and which may have implications for ontogeny related changes or medicinal products with multiple development options to address significant unmet paediatric need in several paediatric indications where adult data are lacking.

These examples are not exhaustive and will be adapted according to experience gained with the new concept and may actually be characteristic of many drug developments for children and therefore would not automatically render a procedure eligible for the sPIP approach.

It may be appropriate to apply for an sPIP when, based on existing scientific knowledge, critical PIP elements such as, for example, those below cannot be defined:

- Study design (e.g., control, randomisation, blinding, endpoints)
- Population (e.g., age subgroups)
- Main objectives (e.g., absence of validated biomarkers or PD endpoints etc.)

Of note, even when a stepwise PIP is not considered appropriate (e.g. when the paediatric development plan can be mostly defined) it is possible to include stepwise elements (e.g. when the dose cannot yet be defined).

2.2. sPIP – practical aspects for submission

- Template
 - The same templates are to be used for every PIP (conventional PIP or sPIP).

For the submission the applicant should indicate the request for a sPIP approach in Sections 2 and 4 of the PIP application as detailed below.
- Application summary
 - It is expected that applicants will provide a high-level summary of the parts/measures/elements of measures of the application following the sPIP approach with a scientific justification for why the sPIP approach is necessary. At a minimum the initial application should contain the condition, preliminary outline of planned studies based on available evidence and a PIP completion date.

- Section 2
 - A valid scientific justification should be provided to support an sPIP approach in the development in all paediatric ages or in certain age subgroups. Applicants are expected to expand on the information provided in the application summary and explain the information gaps and why some studies cannot be planned or why some aspects of the clinical studies cannot be determined or estimated at the time of the initial application. In this part a detailed discussion on existing information (or lack thereof) is expected.
- Section 3
 - No changes are expected here unless details of the waiver cannot be defined (e.g., the appropriate age cut-off). In these cases, a justification on why certain elements of the waiver request cannot be defined at this stage and information on how the data will be generated to define these elements should be provided.
- Section 4
 - In the cases when an sPIP approach is used, not all the measures and/or elements of the measures can be completed at the initial application. Nonetheless a high-level, overall plan and strategy for paediatric development should be included (at a minimum the condition, preliminary outline of planned studies based on available evidence and a PIP completion date) even if it is not possible to include all details. There should be a clear commitment towards milestones/timelines for subsequent PIP modification(s) and outline of how the missing data will be generated and the PIP fully completed. All the open sections, as applicable, will be discussed and agreed upon in future modification procedures to develop the final full PIP.
- It should be clear from the submission which data will be needed to define a certain key element, how these data will be generated and when the data can be expected to be available.
- The timelines proposed and then agreed with PDCO should be linked to milestone(s) such as the completion of a study in adults (e.g., 'a request for modification of the agreed PIP must be submitted within a pre-defined period of time e.g. x months after completion of study y with the aim to agree on this key element'). Specific dates (month and year) or ranges of up to six months can be given if needed.

3. Modification of an agreed sPIP

Missing or preliminary elements of an agreed sPIP (as outlined above) will be updated via the established procedure of modification of an agreed PIP.

In the application for modification of the agreed sPIP, the relevant additional information that has become available to enable the further development of the PIP should be provided along with a justification for how a given key element should be modified. Not all elements of an sPIP need to be updated in a particular modification at the same time. It is, however, recommended to avoid a multitude of minor modifications and to streamline/bundle modification requests accordingly taking into account the agreed timelines.

For an sPIP if applicable, updated timelines/milestones can be agreed during the modification procedure with the PDCO for the subsequent PIP modifications including the overall PIP completion date (as in 'section 4' above). Given the short timeframe of a modification procedure, in cases where significant updates to the sPIP are requested, a pre-submission meeting with the assessment team is strongly recommended.

4. Compliance check(s)

As the final outcome of an sPIP corresponds with the 'conventional' approach to a PIP, the same concept of compliance check applies.

Only a fully developed and completed PIP can be used to fulfil the requirements of Articles 36 and 37 for the purposes of eligibility for the rewards under the Paediatric Regulation.