

Defining a PIP strategy for a new medicinal product: A step-by-step approach

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Key words

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Abstract

A key step in the preparation of a paediatric investigation plan (PIP) for a new medicinal product is to define the PIP strategy, ie, to define how the studies/data extrapolation/waiver/deferral combination will cover, for each targeted indication, all subsets of the paediatric population. Defining the PIP strategy requires considering very different aspects of the development, registration and marketing plans of the product. This can be done through a systematic step-by-step approach including four sequential stages: defining the applicable paediatric legal framework; outlining the development and registration plans for the medicinal product; assessing the need for a paediatric plan and/or a waiver for each target condition/indication of interest; and assessing the relevance of conducting additional studies to address the paediatric population's specific needs.

Introduction

According to Article 7 of the Paediatric Regulation,¹ a marketing authorisation application (MAA) for a new medicinal product – ie, a medicinal product which is not authorised in the Community – must include the results of studies performed in compliance with an agreed paediatric investigation plan (PIP) and/or a waiver and/or a deferral, which combined, shall cover all subsets of the paediatric population.

Therefore, prior to submitting a MAA for a new medicinal product in the EU, it is now mandatory to:

- Submit an application for a PIP and/or a request for a deferral and/or waiver
- Obtain agreement from the European Medicines Agency (EMA)
- If relevant, the studies which have been agreed in the approved PIP (within the agreed timelines).

The Paediatric Regulation specifies that the PIP application should normally be submitted to the EMA 'not later than upon completion of the human pharmacokinetic (PK) studies in adults'. Nonetheless, due to the relatively recent entry into force of Article 7 of the Paediatric Regulation (26 July 2008), a great majority of pharmaceutical companies have not yet applied for a PIP (or requested a waiver or deferral) even for products which are already well advanced in their development. For firms which have in their portfolio a new medicinal product that is at the end of its development plan and for which a MAA is intended to be submitted in 2009 or 2010, preparation of a PIP application should be a top priority task.

The Paediatric Regulation defines a PIP as 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'. This programme covers the quality, non-clinical and clinical aspects of the development of the drug product, is approved by the EMA Paediatric Committee (PDCA) and is binding on the MAA applicant. Published on 24 September 2008, a Communication from the European Commission² provides detailed information concerning the content and format of PIP applications. It is an efficient guide for the writing of a PIP.

Nonetheless, the structure and content of a PIP application must be customised according to the specificities of the medicinal product in development. Experience shows that, rather

than rushing directly into the writing of the PIP, it is always preferable to outline the PIP strategy first. By 'PIP strategy' we refer to the way in which the PIP application should be articulated, ie, how the studies/data extrapolation/waiver/deferral combination will cover, for each targeted indication, all subsets of the paediatric population in a way that is both acceptable from a regulatory standpoint and in line with the applicant's registration plans and expectations.

Defining a successful PIP strategy for a new medicinal product requires considering very different aspects of the development, registration and marketing plans of the product. This can be done efficiently through a systematic 'step-by-step' approach. The goal of this article is to present such an approach.

Step 1: Is a PIP necessary? Defining the applicable legal framework

Not all products fall within the scope of the Paediatric Regulation. Therefore, the very first point that one must define before entering into any PIP discussion is the legal framework for the product. And the first question to be answered is 'Is my product a medicinal product for human use?' This question may sound trivial but is actually essential: the Paediatric Regulation does not apply to medical devices, nor to veterinary medicinal products.

The legal basis for any PIP is set out in Articles 7, 8, or 30 of the Paediatric Regulation. Schematically, it is necessary to envisage the submission of a PIP application as per:

- Article 7 in the case of a medicinal product which is not yet authorised in the Community.
- Article 8 in the case of an authorised medicinal product for which new indication(s), new pharmaceutical form(s) and/or new route(s) of administration are applied for and in the case this product is protected by a supplementary protection certificate (SPC) or by a patent which qualifies for the granting of a SPC.

- Article 30 in the case of a medicinal product that may already be available on the market for adults only, that is not protected by a SPC or a patent qualifying for the granting of a SPC, and for which indications that are relevant for use exclusively in the paediatric population are developed.

Importantly, according to Article 9, generics, biosimilars, hybrid and well-established use medicinal products, homeopathic and herbal medicinal products are exempt from the obligation to submit a PIP application.

The decision tree in Figure 1 may help in defining the applicable framework for a PIP application.

The remainder of this article focuses exclusively on the definition of PIP strategies for new products falling under the scope of Article 7 of the Paediatric Regulation.

Step 2: Considering the product's development and registration plans

Once you have defined the legal framework and determined *a priori* whether you need to submit a PIP application or not, the overall development and registration plans for the medicinal product must be considered.

Considering that Article 7 of the Paediatric Regulation has only been applicable since July 2008, a large number of new products are already well advanced in their development (ie, well beyond the adult PK studies) and have no PIP approved yet.

For a proportion of these products, several indications are developed concurrently. In this specific case, it is important to note that the PIP application will need to cover all target indications.

Therefore, before going into the details of the paediatric plan *per se*, it is useful to have in mind the 'big picture' of the development of the product and address a number of questions, including:

- Which condition(s) or which indication(s) is (are) targeted for the product?
- What is the stage of development for each target condition/indication?
- What is the current plan for registration of the product, ie, will the different indications be requested at the stage of the initial MAA or will this be done in a sequential manner?

Addressing these questions early is key as it allows one to determine which conditions/

indications need to be discussed in the PIP and how they need to be presented. For example, for a product which is already tested in Phase III clinical studies for indication X and only in Phase II for indication Y, it is likely that part of the clinical programme concerning indication Y will be presented as deferred studies (Part E) in the PIP application.

Step 3: PIP or waiver? Or a combination of both?

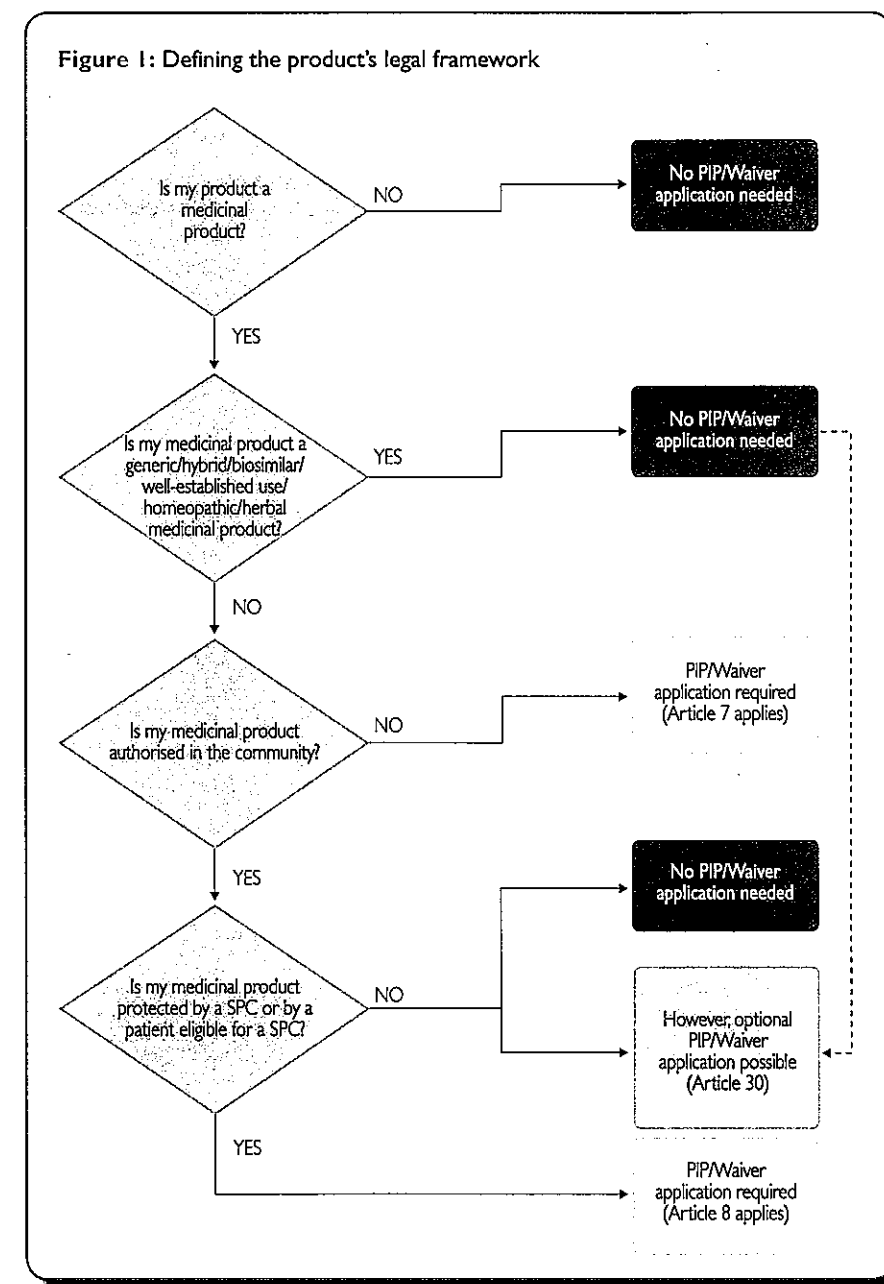
Once a clear view of the registration plan is available the next step is to determine, for each targeted condition/indication, whether

a PIP or a waiver, or a combination of both, needs be submitted to the PDCA for assessment and agreement.

If, for example, you are developing a medicinal product in a condition exclusively targeting the elderly, it is reasonable to think that agreement on a PIP will not be necessary. Indeed, the requirement to submit a PIP can be waived for specific products or classes of products that meet certain criteria, as detailed below.

The PDCA has adopted a list of conditions that occur only in adult populations, referred to as the 'list of class waivers'. All classes of medicinal products intended to treat these conditions

Figure 1: Defining the product's legal framework



are not required to submit a PIP. This list, which was adopted in July 2008, can be found on the EMEA website.³ Most of the conditions in this list are cancers; others include for example amyotrophic lateral sclerosis, Parkinson's disease (non-juvenile) or the treatment of age-related macular degeneration. Note that in one case, a class waiver was adopted for a class of medicinal products: the peroxisome proliferator-activated receptor (PPAR)- γ modulators. In this specific case, the PDCO recommended a waiver on the grounds that this class of medicinal products is likely to be unsafe in all paediatric subsets when used as a treatment of type 2 diabetes mellitus (T2DM). (For this specific class of medicinal products, the PDCO highlighted that children and adolescents with T2DM may have an

increased probability of incurring adverse events than adults, because: a) they have a longer life expectancy than most adult patients with T2DM, and b) effects on growth, including bone growth, and reproduction may be more pronounced than in adults, when the balance between cell proliferation, survival and differentiation is changed due to potent PPAR agonists.)

Therefore, when preparing your PIP strategy you need to verify whether the targeted condition/indication falls under a class waiver status. In such cases, a class waiver confirmation can be sought from the PDCO following a specific procedure.

In the majority of cases, the target condition/indication will not fall under the scope of a class waiver. In this instance, the

next question to be answered is whether another type of waiver applies: this may be a full waiver (ie, covering all paediatric subsets) or a partial waiver (ie, covering one or more paediatric subsets only).

Per Article 11 of the Paediatric Regulation there are only four grounds for justifying a waiver (full or partial). These grounds are:

- The non-occurrence of the disease in one or more paediatric subsets
- The likely lack of efficacy of the medicinal product
- The likely lack of safety of the medicinal product
- The absence of significant therapeutic benefit of the medicinal product over existing treatments for paediatric patients.

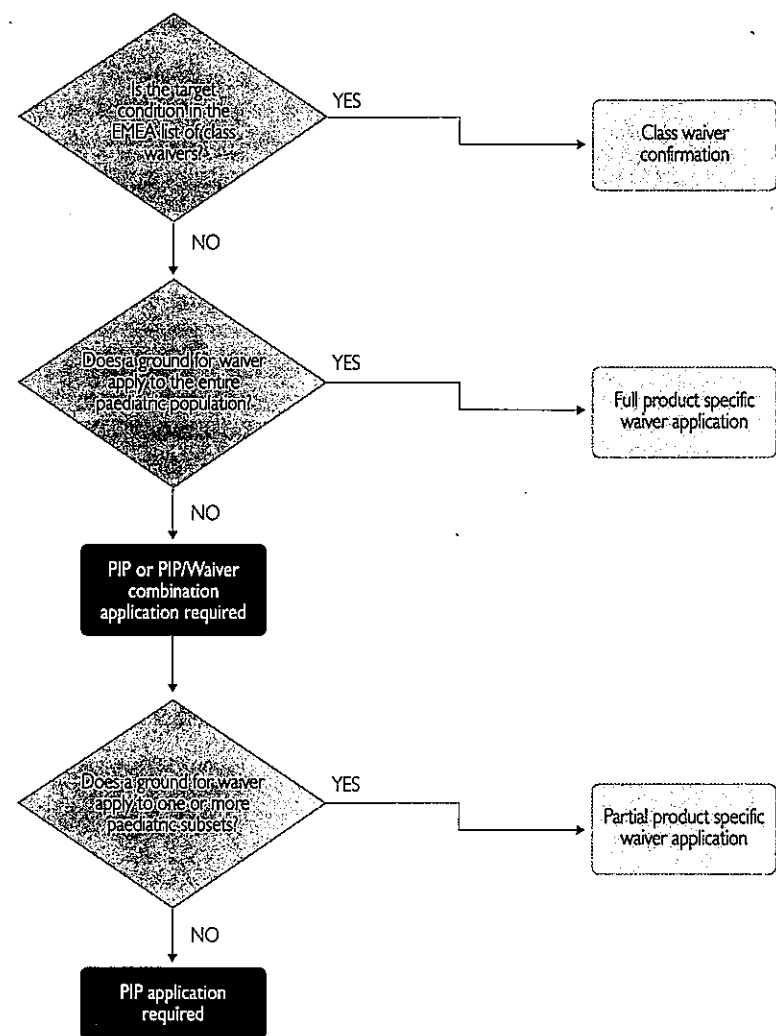
These grounds are not mutually exclusive and may therefore be combined to cover different subgroups of the paediatric population.

The decision tree in Figure 2 can help in defining whether a PIP or a waiver or a combination of both, are required.

Keeping in mind that only these four grounds can be invoked to request a waiver is absolutely key for the person in charge of preparing the PIP strategy. Although a multitude of reasons can be found to justify not conducting paediatric studies during an internal product development team meeting (eg, 'We don't know anything about the pharmacokinetics of our product in children', or 'We don't have a suitable formulation and/or we would need to develop a suitable administration device first', or 'Performing paediatric clinical studies will be difficult and has not been planned'), when it comes to requesting a waiver (full or partial) from the EMEA, only the grounds listed above can be positively considered by the PDCO.

It is important to note that in some cases where the applicant does not request a waiver, the PDCO can grant a waiver on its own motion. This 'forced' waiver may cover some or all subsets of the paediatric population. Based on the review of the product-specific decisions published by the PDCO, so far, the forced waivers which have been imposed on sponsors are mostly based on the ground that the specific medicinal products do not represent a significant therapeutic benefit over existing treatments for paediatric patients. The main impact for applicants in this case is the non-eligibility for the relevant incentives (and also some negative publicity, as all EMEA decisions are published on the EMEA website).⁴

Figure 2: PIP or Waiver? (For each target condition/indication)



At this stage in the definition of the PIP strategy it is important to consider that the paediatric population is not homogeneous, and actually made up of different subsets. Per ICH Topic E11,⁵ the following age groups are defined in relation to developmental stages:

- Preterm newborn infants
- Term newborn infants (0-27 days)
- Infants and toddlers (1 month to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 18 years excluded).

These age ranges reflect standard biological changes and may not always be relevant. It is up to you to define your own specific paediatric subsets and make sure that they are appropriate in the context of the development of your product in the specific target indication. For example, the onset of the targeted disease may be three years, or you might be developing a product that is particularly adapted to treating young children and consider that your product will not bring any significant therapeutic benefit over existing treatments for paediatric patients aged six or more.

Through consideration of all paediatric subsets for each target condition/indication, you will end up with a clear picture of your PIP versus waiver strategy, as illustrated in Figure 3:

- Option 1: A full product-specific waiver
- Option 2: A combination of a partial waiver and a PIP
- Option 3: A full PIP, covering the entire paediatric population.

Step 4: Sufficient data, extrapolation or need for new studies?

For each target condition/indication, after having defined all paediatric subsets for which a PIP will be necessary (and for which sufficient data will need to be presented to determine the conditions in which the product may be authorised to treat these subsets), the next step consists of assessing whether particular studies (covering the quality, nonclinical and clinical fields) will need to be carried out or not.

In some cases, clinical data generated in one particular subset of patients (for example in adults) are sufficient to cover a broad population (including paediatric patients) as extrapolation of these data (PK, PD, efficacy and/or safety) is possible. Unfortunately, there is no general rule for determining

Figure 3: Defining the PIP strategy (For each target condition/indication)

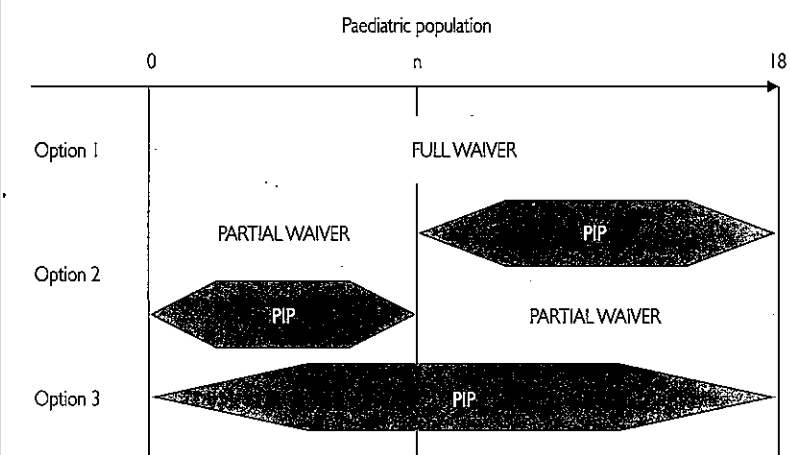
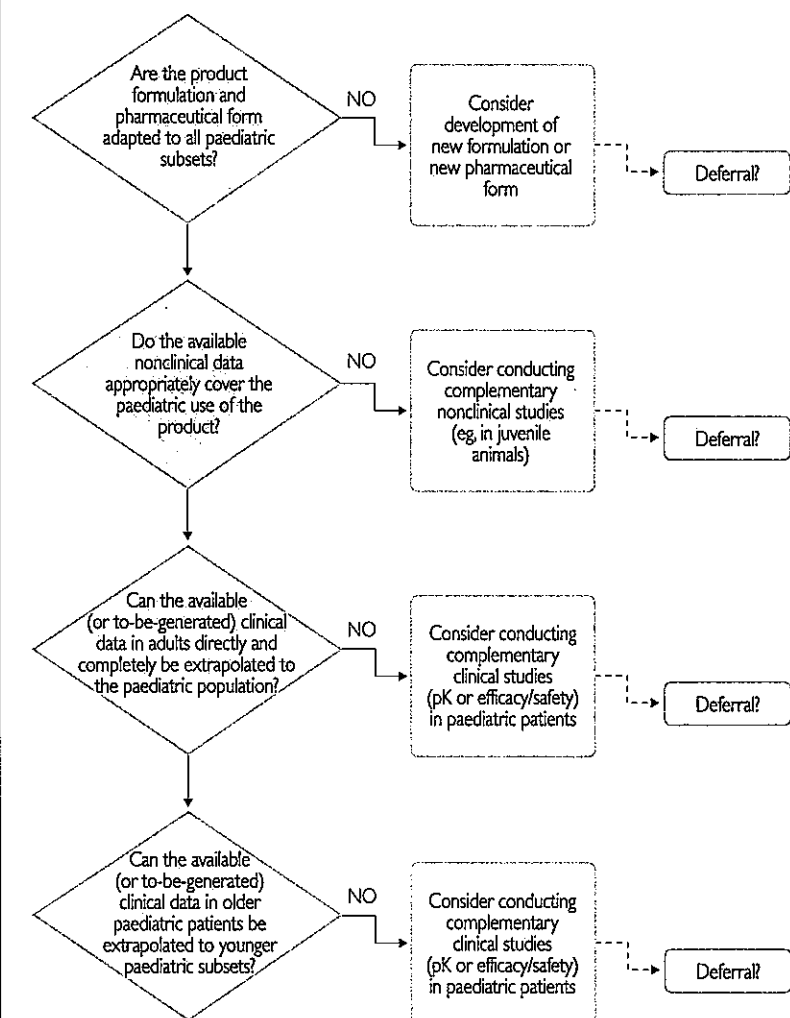


Figure 4: Need for new studies? Now or later? (For each target condition/indication and each paediatric subset)



whether it is possible to extrapolate existing data (especially clinical data) from the adult to the paediatric population or from an older paediatric subset to a younger one. This needs to be considered on a case-by-case basis and usually requires the involvement of different experts (including, for example, clinicians, toxicologists, pharmacokineticists, paediatricians).

For each target condition/indication, and each paediatric subset, you should therefore consider all developmental aspects related to the paediatric population, and obtain responses to all of the following questions:

- Are the product formulation and pharmaceutical form adapted?

- Do the available nonclinical data appropriately cover the paediatric use of the product?
- Can the available (or to-be-generated) clinical data in adults be extrapolated directly and completely to the paediatric population?
- Can the available (or to-be-generated) clinical data in older paediatric patients be extrapolated to younger paediatric subsets?

If the response to one or more of these questions is 'No', it is likely that additional studies will be required to address the specific paediatric needs.

The decision tree in Figure 4 can

help determining the potential need for additional studies.

Step 5: New studies – Can they be deferred?

In the event that new studies are deemed necessary, the next step will be to define whether these additional studies can be deferred or not. Indeed, pursuant to Article 20(1) of the Paediatric Regulation, at the same time as the PIP is submitted, a request may be made for deferral of the initiation or completion of some or all of the measures set out in that plan.

When considering the development and registration of a new medicinal product, requesting a deferral for one study means that the results of this study will not be available at the time of the initial MAA submission and will therefore be provided later.

It must be noted that requests for deferrals should be justified on scientific and technical grounds or on grounds related to public health. Specifically, the Paediatric Regulation foresees that a deferral may be granted in two specific cases:

- When it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population (ie, to increase global knowledge on the product, in particular related to its safety).
- When studies in the paediatric population will take longer to conduct than studies in adults (ie, to avoid delaying the submission of the MAA of the product for the adults).

Economic constraints should not be invoked as a reason for requesting a deferral. A sponsor's position based on this ground would not be considered positively by the PDCO.

Step 6: Finalising your PIP strategy

At the end of the step-by-step process, you should end up, for each target condition/indication, with a clear view of the different possible combinations of waiver/deferral/studies (or extrapolated data) that may cover the full paediatric population.

Finalising the PIP strategy consists of choosing the most appropriate of these combinations. While taking into account the applicant's registration priorities, this choice should mainly be guided by the availability of strong scientific and/or technical justifications supporting one or the other combination.

Figure 5 illustrates various possible

Figure 5: Defining the PIP strategy (For each target condition/indication and each paediatric subset)

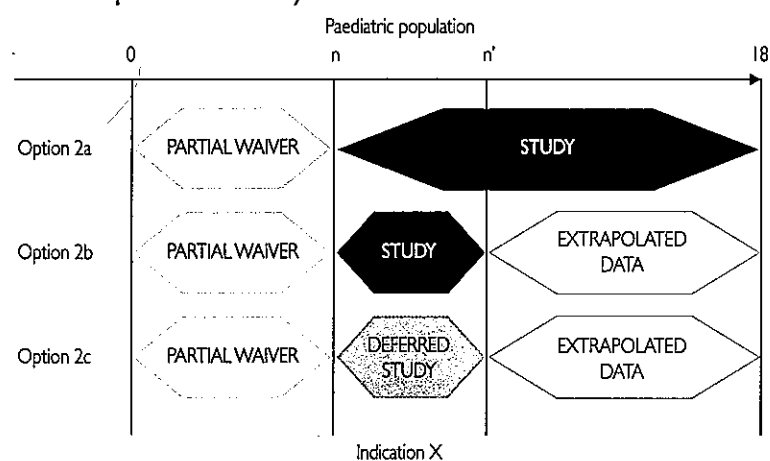
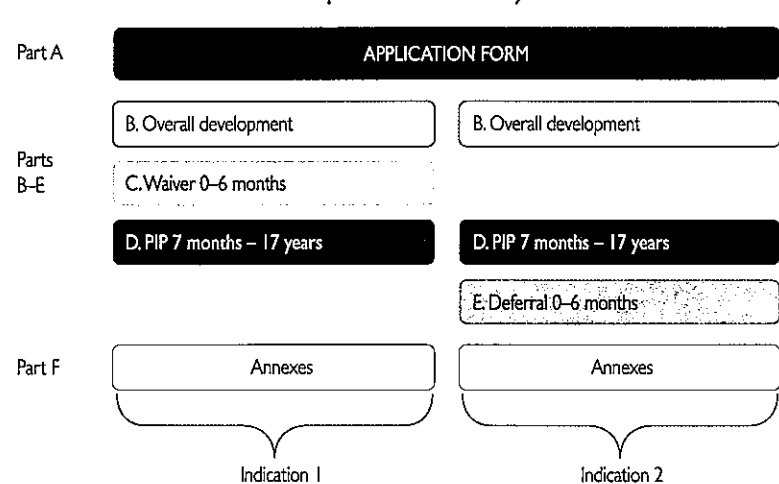


Figure 6: Defining the PIP structure (covering all target conditions/indications and all paediatric subsets)



combinations, considering a 'partial waiver + PIP' strategy (option 2 of Figure 3).

As already mentioned above, the Paediatric Regulation requires that, when it is intended to develop several condition(s)/indication(s) simultaneously, only one comprehensive PIP should be submitted. Therefore, after defining the most appropriate PIP strategy for each indication, you will obtain a clear picture of the PIP application structure you need to prepare and submit. An example of PIP structure is provided in Figure 6: all target conditions/indications (here we have two) and all paediatric subsets (here we show two, which are identical for both indications) are covered.

Conclusion

Defining your PIP strategy can be broken down into four sequential stages, based on four essential items which need to be thoroughly examined:

- Defining the applicable paediatric legal framework.
- Outlining the development and registration plans for the medicinal product.
- For each target condition/indication

of interest, assessing the need for a paediatric plan versus a waiver, or a combination of both.

- Assessing the relevance of conducting additional studies to address the paediatric population's specific needs, and the associated timelines. During these assessments, all paediatric subsets and all target conditions/indications should be addressed and appropriately covered.

While submitting a PIP application is a regulatory activity, designing an appropriate PIP strategy requires input from all parties involved in the product's development, ie, the technical experts (CMC, nonclinical, clinical and regulatory) but also the management, as once approved, a PIP decision is binding on the MAA applicant.

Common sense and pragmatic thinking are critical in the definition of the appropriate PIP strategy as this may become a challenging task. A systematic step-by-step approach such as the one described in this article can help in this exercise, especially when, for a new medicinal product, several indications are developed simultaneously.

References

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