Writing applications for Paediatric Investigation Plans and waivers

Paolo Tomasi

Paediatric Medicines, European Medicines Agency, UK

Correspondence to:

Paolo Tomasi,
Paediatric Medicines,
European Medicines Agency, London, UK
paolo.tomasi@ema.europa.eu

Abstract

Under EU legislation, a Paediatric Investigation Plan (PIP) and/or a waiver must be agreed in advance with the European Medicines Agency (EMA), for all new medicinal products seeking marketing authorization; the same applies for already authorized products under certain circumstances. In principle, the application needs to be submitted early in the development (before completing basic Phase I studies in adults), which may require an innovative and creative approach to the drafting of the necessary documents. The aim of this article is to provide a guide on already existing and available help and advice, to provide further suggestions and comment, and to illustrate common mistakes; the reader should then be able to increase the chances of a more rapid procedure with a higher probability of a positive outcome of the procedure.

Keywords: Paediatric Investigation Plan, Waiver, Deferral, EMA, Application, Guideline

Introduction

The EU Regulation 1901/2006 (http://bit.ly/tth2CD) – the 'Paediatric Regulation' – provides a systematic approach to the development of medicinal products intended for use in the paediatric population. This legal framework followed the first US initiative (the Best Pharmaceuticals for Children Act), which has been in place since 1997. Pharmaceutical companies are now required to perform clinical studies in children before being able to apply for marketing authorization of a new medicinal product in the EU (or for a new indication, dosage form or route of administration of an authorized, patented product), unless they have agreed a waiver or a deferral with the Paediatric Committee (PDCO) of the European Medicines Agency (EMA).

The Paediatric Investigation Plan

Companies are required to agree with the PDCO of the EMA on the proposed studies and measures to be undertaken for a new medicinal product; this constitutes the so-called Paediatric Investigational Plan (PIP).

A PIP should provide sufficient data to enable the assessment of the quality, safety, and efficacy in children, and consequently the benefit/risk profile in the paediatric population.

When preparing a PIP, the six core questions to be addressed are the following:

1. Is there a need for the candidate medicinal product in children?
2. If there is a need for paediatric development, what is the condition(s) in which paediatric development should occur, considering the proposed indication(s) in adults?
3. In which age group(s)/paediatric subsets should the development take place?
4. Should there be an adapted formulation and a specific non-clinical package?
5. What clinical measures should the paediatric investigation plan contain?
6. Should any measures in the PIP (mainly clinical trials in children) be deferred or not?

If an agreed PIP becomes no longer feasible, or inappropriate due to new scientific knowledge, applicants can always request one or more modifications to the agreed PIP.

Deferrals

Deferrals are the instrument to avoid a delay in marketing authorization in adults. In many cases (but certainly not always), paediatric studies can or should be performed after studies in adults have confirmed the activity and the safety of the product; a deferral to initiate or complete one or

DOI: 10.1179/2047480612Z.00000000021

more studies in children may therefore be requested and agreed by the PDCO.

Waivers

Some conditions do not occur in children, or in some subsets of the paediatric population. Therefore, a waiver from the obligation to do studies can be granted by the PDCO. In addition, waivers may be granted when the medicinal product is expected to be unsafe or ineffective in children (or in subsets), and finally when the product appears to have no significant benefit at all over existing treatments for the same condition. Applicants are expected to thoroughly justify, with supporting evidence, any request for a waiver, whether 'partial' (specific subsets of the paediatric population) or 'total' (applying to all paediatric subsets in a given condition).

Available guidance

A presentation on the resources available to applicants, when developing a PIP or waiver application, is available on the EMA website (http://bit.ly/xO1T9y).

More specifically, the official European Commission (EC) Guideline on the format and content for PIP and waiver applications and for compliance check is published on the European Commission's website (http://bit.ly/EC-PIP-guidance). This is the basic guideline that contains all the necessary information on what a PIP/waiver application needs to contain, and is fundamental reading for anyone preparing an application.

While the EC guideline mainly addresses scientific aspects and the content of applications, the various procedural aspects are contained in the questions-and-answers document published on the EMA website (http://bit.ly/PIP-Proc-Advice). This contains a pot-pourri of technical and regulatory issues that have arisen most frequently during interaction with applicants; of particular relevance to the preparation of the PIP application are questions 6, 8, and 9. This guidance is also a must-read, particularly before addressing a question to the EMA, as in most cases it will have been covered already in the published answers.

Any document in the EMA website, including scientific guidelines, can be found with the EMA search engine (http://bit.ly/wtOCmL); additionally, specific preselected lists of guidelines of paediatric interest are also present (http://tinyurl.com/paedguidelines, http://tinyurl.com/paedguidelines2). Among the most recently published ones, the following have particular relevance: the Draft guideline 'Pharmaceutical Development of Medicines for Paediatric Use' (http://tinyurl.com/draftqualitypaeds), and 'Investigation of medicinal products in the term and preterm neonate', (http://tinyurl.com/EMAneonates).

The EMA periodically organizes Expert Groups on topics of relevance for the development of paediatric medicines; presentations and outcomes are published on the website (http://tinyurl.com/PaedExpGroups).

EMA Decisions on PIPs and waivers, including modifications, are also published and searchable by condition (http://tinyurl.com/PIPDecisions).

Points to consider

Adequate justification is of paramount importance

It is crucial that every request/proposal (for a PIP, for a deferral, a waiver, a specific study…) be properly justified in the PIP application. The PDCO has negatively viewed several PIP/waiver applications, not because the proposals of the applicant were unacceptable in principle, but because they were not properly justified. This meant that there were not enough elements to assess whether the proposal was acceptable or not.

One PIP or multiple PIPs?

In some situations, when a product is being developed for more than one condition in adults, and the marketing authorization procedures will be separate, it will be convenient to ask two separate PIPs for the same medicinal product, one per condition. This may allow, again under certain circumstances, an earlier reward. Guidance will be published in the EMA website, within Q2 2012, to clarify these aspects.

Mechanism of action

It is important to describe, in sufficient detail, the putative mechanism of action of the product. The condition for paediatric development is identified by the PDCO also based on the mechanism of action, starting from the proposed indication (in adults).

Pharmaceutical form(s)/quality aspects

These are to be provided in the application form (Part A) rather than in the scientific documents (Parts B–E). Again, a sufficient level of detail needs to be provided.

Role of extrapolation

Most paediatric investigation plans contain at least some form of 'partial' extrapolation, in the sense that the scale of the development (number of studies, number of patients, etc.) is different from what is done in adults. This rests on the assumption

of at least some similarity in response between adults and children with the same/analogous disease. However, no matter the degree of extrapolation (in some case, it may be acceptable to completely extrapolate efficacy), applicants should be explicit in the justifications for the amount of extrapolation proposed. The EMA has a working group on extrapolation, and the outcomes will be published on the website, starting in 2012.

Presubmission meetings

The EMA accepts requests for presubmission meetings from prospective applicants, with a view to improving the quality of the application to be submitted and increase the chances of a smoother validation and a final positive opinion at the PDCO. Details about these meetings are available on the Q&A document on the EMA website (Q&A 26 in http://tinyurl.com/PIPQ-A).

Frequent mistakes/ misunderstandings

Some misunderstandings seem to occur with greater frequency, and therefore a brief discussion of them is provided here.

- *Insufficient information provided*: Whether in Part A (application form), or in Parts B–E (scientific document), this is likely to lead to non-validation.
- *Excess information provided*: There is no need to provide a detailed discussion of the disease, as can be found in textbooks, for common disorders.
- *Justification*: As already mentioned, providing sufficient justification is crucial, particularly when requesting a waiver or a deferral. For example, it is not sufficient to simply state that a disorder is rare in children, and therefore studies are not feasible, to obtain a waiver. In such cases, a prevalence analysis should be carried out, supported by available literature evidence, expert opinion etc.
- *Deferral*: A frequent source of confusion. When a deferral is requested for, say, completion of a given study, this just means that marketing authorization (MA) in adults can be sought before completing that particular study in children; it does not exempt the applicant from proposing justified and sufficiently detailed elements about how the study will be. Furthermore, even a deferred study must include a proposed completion date (an 'absolute' date, not relative to the foreseen date of application for MA), and after that date the study will become due, even if, for whatever reason, the application for MA in adults has been postponed.
- *Pharmaceutical form*: While it is understood that not all quality aspects of the product for paediatric use will be known at the time of the application, the applicant still needs to provide a proposal of what will be developed, with sufficient details to allow the PDCO to express an evaluation of the proposal itself.
- *Non-clinical development*: In this section of the application, an explicit discussion of the possible need of studies in juvenile animals should be included. The Non-Clinical Working Group of the PDCO will assess all relevant PIP proposals, to this aim.
- *Clinical studies*: The opinion, to be adopted by the PDCO, will not contain the full details of each study protocol for the clinical trials, but only the key elements, on which compliance check will be done at a later stage. Often applicants are surprised to receive a 'slim' opinion, lacking many of the elements in the full protocol, and request that they are reintroduced: this is not necessary and actually can be counterproductive, as a modification of an agreed PIP may become necessary to change secondary elements of the protocol.
- *Coverage of all paediatric subsets*: All paediatric subsets must be covered in the applications, either with PIP studies, or with a (partial) waiver. A common mistake is the omission of a small subset (say, from 4 to 6 years of age) from the PIP/waiver. In principle, whenever there is a paediatric need, a waiver is inappropriate, and that paediatric subset must be covered by one or more studies in the PIP. Studies may include extrapolation studies.
- *Methodology*: A single-arm, open label study cannot demonstrate efficacy. At best, it can support a claim of activity (usually on a biomarker or surrogate endpoint). That is not to say that these studies are always unacceptable, but proper justifications need to be provided. Also, a commonly encountered omission is the lack of a power analysis/sample size determination, again without justification. While it is acknowledged that rare conditions will be even rarer in children, and that fully powered, controlled efficacy studies are not always possible in children, this does not necessarily imply that a waiver will be granted under these circumstances: limited data on activity and tolerability/safety in small samples may be

acceptable, in some circumstances and again with proper justification. Other common mistakes include: specifying multiple primary endpoints without the correct methodological approach, too wide delta for non-inferiority studies, mixing too many objectives (Phases I, II, and III in the same study), etc.

Conclusion

A well-written PIP is central to a rapid validation, and increases the chances of a positive opinion by the PDCO. Several resources are available in the EMA website, and specifically in the two paediatric sections (Regulatory/Paediatric Medicine and Special Topics/Medicines for children); in addition, draft applications can be discussed for further advice during a presubmission meeting. While in paediatric medicines trials may be small, the evidence still needs to be good: the goals of the paediatric regulation include an increased availability of authorized medicines for children, and to this end, the approval of a suitable paediatric investigation plan is a necessary first step.

Author information

Paolo Tomasi (MD PhD) has been Scientific Administrator at the European Medicines Agency since 2006, and Head of Paediatric Medicines since 2009. He is a clinical specialist in endocrinology, and assistant professor of Internal Medicine at the University of Sassari, Italy. He is author/coauthor of >40 publications in Medline.