Preparing the Paediatric Investigation Plan application

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Abstract

In Europe, sponsors must possess a compliant Paediatric Investigation Plan (PIP) when applying for marketing approval of drugs. The core deliverable is the 'scientific part of the application' structured according to the EMA's PIP guideline. The PIP should summarize relevant background information on the disease and drug, and use this to justify a paediatric development programme that covers the entire paediatric population. Depending on the type of drug and the relevance of the disease to the paediatric population, specific quality, safety, and/or efficacy measures may be proposed for all or part of the population. If measures are considered inappropriate for all or part of the paediatric population, then a waiver may be proposed but must be justified. If the paediatric development programme cannot be completed before submission of the adult application, then a deferral of the paediatric measures may be proposed but again this must be justified. In any case, a detailed timetable has to be provided and adhered to for any all measures being proposed. The main challenges for medical writers when writing a PIP are application of the guidance to the drug and disease in hand, and obtaining the appropriate input from the project team.

Keywords: Paediatric Investigation Plan, Waiver, Deferral, Paediatric measure, Application

Since enforcement of the Paediatric Regulation in 2007,[1] sponsors must possess a compliant Paediatric Investigation Plan (PIP) when applying for marketing approval of unauthorized drugs, or when applying for approval of new indications, pharmaceutical forms, or routes of administration for currently authorized drugs. The default situation is that a Marketing Authorization Application (MAA) should now include findings from the paediatric population. These findings have to be obtained in clinical studies designed and conducted according to measures described in a PIP that was agreed upon beforehand by the European Medicines Agency (EMA)'s Paediatric Committee (PDCO). Because the Paediatric Regulation also stipulates that an MAA should not be delayed due to a paediatric development programme, there are also provisions for deferring or waiving some or all paediatric measures, as described below.

The core deliverable for a PIP application is the 'scientific part of the application', which is a document structured according to the EMA's PIP guideline.[2] A length of 'below 50 pages' is recommended, which sounds brief and can lead sponsors preparing a PIP for the first time to underestimate the time and effort required. With this in mind, and assuming the need for a PIP has been established, there are six main steps involved in preparing a PIP application, as outlined in the sections that follow.

Consult the guideline and associated resources

The final guideline on the structure and content of a PIP was published in September 2008. At first sight this is not a particularly user-friendly document. For example, it often refers to specific articles of the paediatric regulation that themselves are sometimes challenging to interpret. Fortunately, the EMA's website provides a number of other sources of information that can help in preparing a PIP. Foremost among these are the *Electronic form for paediatric investigation plan application and request for waiver* (a PDF file sometimes referred to as the 'PIP template') and the *EMA/PDCO summary report template with internal guidance text*.

A common misconception is that the PDF file referred to above is a template into which text can be inserted for the entire PIP application. This is not the case. Instead, this is a dynamic PDF file that covers Part A of the PIP application. It addresses administrative aspects such as details of the

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applicant, the drug, the intended indication, etc. However, at the end of the file is a table of contents that provides the recommended high-level structure for the scientific part of the application (i.e. including the 'scientific part of the application' in Parts B–F). Confusingly, the suggested structure is not identical to the organization provided in the final PIP guideline, but fortunately the difference lies only in the order in which information is provided.

Thus, based on the table of contents given in the PDF file, applicants can create their own templates in a Word file for writing Parts B–F of the application. The high-level structure suggested by the EMA is shown in Table 1, which in practice will need to be augmented with subsections tailored to the specifics of the application.

The *EMA/PDCO summary report template* is used by EMA reviewers to write their assessment reports, which are then used by the PDCO to review the application. The template is helpful for applicants because it provides recommendations on what reviewers should assess and provide comments on. Thus, by addressing these issues during authoring of the PIP, the writer can tailor the PIP's content to the PDCO's expectations and potentially reduce the number of questions arising during review.

Plan resources and timelines

As with other regulatory documents, realistic planning of resources and timelines is crucial to the timely success of preparing the PIP. Writing a PIP almost always requires more resources and time than initially estimated. This can be partly due to a lack of experience, and partly because PIPs often need to include substantial amounts of text drafted anew rather than text adapted from existing material. As discussed below, such texts include background information on the paediatric population and the disease at hand (which can be difficult to obtain) and the rationale for the measures that constitute the paediatric development strategy (which typically involves lengthy discussions and multiple revisions).

Table 1: Recommended structure of the PIP according to the 2008 EMA guidance in the 'Application for Paediatric Investigation Plan/Waiver' (Version 3.0.0)

PART B – Overall Development of the Medicinal Product Including Information on the Target Diseases/Conditions
B.1 Similarities and Differences
B.1.1 Discussion on similarities and differences of the disease/condition between populations (including information on prevalence/incidence)
B.1.2 Pharmacological rationale and explanation (including structure, absorption, PK, pharmacodynamics, metabolism, elimination; mechanism of action; similarities and differences of the safety and efficacy profile)
B.2 Current Methods of Diagnosis, Prevention or Treatment in Paediatric Populations
B.3 Significant Therapeutic Benefit/Fulfilment of Therapeutic Needs
PART C – Applications for Product Specific Waiver(s)
C.1 Overview of the Waiver Request(s)
C.2 Grounds for a Product Specific Waiver
C.2.1 Grounds based on lack of efficacy or safety
C.2.2 Grounds based on the disease or condition not occurring in the specified paediatric subset(s)
C.2.3 Grounds based on lack of significant therapeutic benefit
PART D – Paediatric Investigation Plan
D.I Existing Data and Overall Strategy Proposed for the Paediatric Development
D.I.a Paediatric Investigation Plan indication
D.I.b Selected paediatric subset(s)
D.I.c Information on the existing quality, non-clinical and clinical data
D.II Quality Aspects
D.II.a Strategy in relation to quality aspects
D.II.b Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development
D.III Non-clinical Aspects
D.III.a Strategy in relation to non-clinical aspects
D.III.b Overall Summary Table of all non-clinical studies
D.III.c Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies
D.IV Clinical Aspects
D.IV.a Strategy in relation to clinical aspects
D.IV.b Overall Summary Table of all clinical studies
D.IV.c Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies
D.V Timeline of Measures in the Paediatric Development Plan
PART E – Request for Deferral(s)
PART F – Annexes

The resources required will depend on the applicant company's size and structure. In general, the core team should include at least a regulatory coordinator and an experienced medical writer, together with representatives from the CMC, nonclinical, and clinical functions, and a publisher to compile the submission package. While different functions may contribute materials for their subject areas, including texts that can be 'just added to the document' (beware, experienced medical writers will know that such texts invariably need extensive reworking), experience has shown that the medical writer's input is invaluable in ensuring consistency of content between the different sections. The medical writer's oversight is also essential for maintaining an overview of material still required and by when it will be needed if the envisaged submission date is to be maintained.

The submission date for the PIP application will usually be linked to one of the monthly PDCO meetings in the overall context of the anticipated date for the MAA submission, by which time a compliant PIP is required. Planning back from the MAA submission, it is prudent to plan for questions that will need to be addressed after initial submission of the PIP. Realistically, it can take at least 6 months between submitting the PIP and obtaining agreement on the paediatric measures contained therein. The time taken to prepare the PIP will depend on the resources available and the extent of information to be included. Even when a project is well resourced, considering the time needed for literature searches, obtaining advice on the paediatric strategy, authoring, at least two rounds of review, finalization, and compilation (including annexes in Part F), a time frame of around 6 months is realistic for preparing a submission-ready PIP. Thus, the time between starting to prepare a PIP and obtaining agreement from the PDCO can easily extend to a year (sometimes longer).

Summarize information on the drug and the intended indication

In Part B, the applicant has to provide background information to support the rationale for the proposed paediatric strategy described later on in Parts C and D. The most challenging part to write is generally Part B.1, which provides information on the disease to be treated and the expected performance of the drug (or class of drug). Specifically, the guideline stipulates information on known and expected similarities and differences between adult and paediatric populations, and between different age categories within the paediatric population (e.g. as suggested by the ICH E11 guideline, see Table 2). Topics to be covered include characteristics and seriousness of the disease, prognosis, epidemiology, the drug's pharmacological properties and mechanism of action, and known or expected safety and/or efficacy information related to the mechanism of action. Phase I clinical pharmacology data should be included in Part B.1, but safety and efficacy data for the drug from clinical studies in adults should be summarized in Part D.

Table 2: Categorization of the paediatric population according to the ICH E11 guideline

Paediatric category	Age
Preterm newborn infants	Preterm
Term newborn infants	0–27 days
Infants and toddlers	28 days to 23 months
Children	2–11 years
Adolescents	12–16 or 18 years, dependent on region

Bearing in mind that the paediatric population is highly diverse, the difficulty often encountered by writers is obtaining the appropriate information for Part B.1 to cover all age categories. In terms of disease characteristics and epidemiology, a literature search is often required, which can be time-consuming and therefore expensive. At kick-off meetings for PIPs, it is not unusual for medical writers to be told something like 'all the information is available in the Investigator's Brochure'. This is rarely, if ever, the case. The medical writer is therefore often left needing to educate the team about this important section, the purpose it serves, and, depending on the indication involved, the often considerable effort needed to research the relevant information and summarize it at the appropriate level for a PIP.

Position the drug in the spectrum of therapeutic options

In Part B.2, a review of current methods of diagnosis, prevention, and treatment in paediatric populations for the disease at hand is required. Again, this section might require some literature search as well as consultation of regulatory information and drug approvals, as available on the Internet. The key elements to be summarized include current treatments and standard of care options across the entire paediatric population and how the applicant's drug compares with these options. If applicable, information in this section would also be used to

justify the options for active comparators in the proposed clinical studies.

Against the background of the information in Parts B.1 and B.2, the applicant has to provide a justification in Part B.3 for the anticipated therapeutic benefit of the drug. The key questions here are whether the drug is expected to provide improved safety or efficacy compared to current therapeutic options in some or all of the paediatric population, or whether comparable efficacy or safety are expected but with an improvement in quality of life due to, for example, an improved dosing regimen or an age-appropriate mode of administration.

Provide a convincing rationale for the paediatric strategy

Supported by the considerations in Part B, the applicant will need to crystallize a paediatric strategy that is acceptable to the PDCO. A primary aim of the Paediatric Regulation is that clinical studies should be designed and conducted to provide paediatric data that can be used as the basis for the drug's prescribing recommendations. However, depending on the type of drug, the nature of the disease, and the epidemiology of the disease across the paediatric population (i.e. as described in Part B), the applicant may instead decide upon a strategy that includes proposing a waiver and/or a deferral for measures in some or all of the paediatric population. A waiver (to be described in Part C) means that the applicant proposes not to conduct paediatric measures, i.e. clinical or nonclinical studies, or testing of an age-appropriate formulation. A deferral (to be described in Part D) means that paediatric measures are proposed but that their completion and reporting are to be delayed, generally with respect to the timing of an MAA submission for adults.

In some cases, a waiver for the class of drug (as published by the EMA) may be applicable and the applicant can refer to this in the rationale for not conducting paediatric studies in some or all age categories, or for specific indications. This does not absolve the applicant from submitting a PIP, even if a class waiver covers all age categories. Class waivers published by the EMA are typically available for drugs used to treat diseases occurring only in adults, or where there is reason to believe that the class of drug is unlikely to have adequate efficacy or safety in paediatric patients. In addition, product-specific decisions published by the EMA may also provide insight from similar types of drugs with regard to whether a waiver may be appropriate for the applicant's drug. Waivers will only be granted by the PDCO when the applicant can make a convincing case that paediatric measures are not warranted. An applicant's lack of interest in conducting a development programme for some or all of the paediatric population is not an acceptable reason for proposing a waiver.

The application for a deferral is product-specific and is generally driven by practical considerations such as availability of an age-appropriate formulation of the drug, the need for further nonclinical studies, or the requirements of a global clinical development strategy (e.g. driven by the availability of data from other regions).

A common situation is that the applicant proposes paediatric measures for at least part of the paediatric population, and a waiver for the remainder of the paediatric population. For the writer the challenge is to craft a convincing rationale for the design of these measures that harmonizes with the background information provided in Part B. This is not trivial because there is often an inherent tendency by applicants to propose a minimal number of measures, and such an approach may be difficult to align with the information provided in Part B and may also contradict the PDCO's somewhat academic approach to the need for paediatric measures. The result is that rationales for waivers (in Part C) and proposed paediatric measures (in Part D) usually result in a high degree of iteration between the medical writer and other team members over a period of several weeks before the texts are agreed upon by all. To a lesser extent the same is also true for the rationale for a deferral provided in Part E.

In Part D of the PIP, which is the core of the 'plan' being proposed, the descriptions of the paediatric measures to be conducted are preceded by summaries of existing information relevant to the drug's formulation and its nonclinical and clinical development. In terms of clinical development, this section should provide an overview of existing data on the efficacy and safety of the drug obtained in clinical studies in adults. However, clinical pharmacology data should not be provided here because this information will already have been summarized in Part B.1 in the context of the drug's pharmacological properties and mechanism of action. If necessary, cross-references back to information summarized in Part B should be used.

The paediatric measures being proposed, in terms of 'quality' (e.g. development of an age-appropriate formulation) and nonclinical as well as clinical studies, need to be specific in terms of

strategy and method descriptions (the EMA provides a PDF template for synopses of nonclinical and clinical studies) as well as timelines. Here the writer is often confronted with the team's desire to be as noncommittal as possible. However, anecdotal evidence consistently suggests that the PDCO requires specific descriptions of measures that may be conducted several years in the future, including details of statistical analyses. Furthermore, the timelines for all proposed measures need to be specified in relation to the submission date for the MAA. The timelines have to be defined to at least the nearest quarter year and are binding, meaning that after agreement on the PIP has been obtained they may only be changed via the laborious procedure of a PIP amendment. The details of the paediatric measures and their timelines are usually the subject of intense discussion within the team. The writer can play an important role in ensuring that the measures being proposed are aligned across different functional areas and within the overall context of the background information on the drug and the disease presented in Part B.

Complete the PIP package

Even after the team has reached an agreement on the content of Parts B–E, time still needs to be planned in to complete the PIP package through to submission readiness. This is the time when the content is now stable and the writer can finalize technical issues such as formatting, cross-referencing, and consistency of language. There are also a number of technical requirements specified by the EMA that need to be taken care of, such as removing active hyperlinks to references or tables and figures, and ordering the list of published literature at the end of the PIP alphabetically.[3]

The annexes in Part F will also need to be completed during this time. In addition to providing copies of all published literature referred to in Parts B–E, the annexes should also include other relevant reference materials where available, such as an Investigator's Brochure, a Risk Management Plan, product information if the drug is already approved, any opinions and/or decisions received for the drug from regulatory authorities, and any official scientific advice received on the drug. Although the annexes should ideally be compiled as far as possible while the PIP texts are being drafted, in practice a large part of this task is often completed shortly before submission and careful planning is needed to avoid this becoming a rate-limiting step. The services of a publisher are required for electronic compilation of a PIP submission, and in practice the medical writer also acts as an interface between the publisher and the rest of the team for resolving last-minute issues before the PIP application is ready for submission.

Conclusions

The PIP is a relatively new type of regulatory submission document that many applicants still have little or no experience of preparing. Depending on the drug and the disease at hand, the PIP can be a demanding document to write and the effort required in its preparation is often underestimated. An experienced medical writer can play a key role in helping applicants interpret the requirements of the PIP guideline so that team members can provide the required material and scientific guidance needed for writing the various sections of the PIP. Ultimately, by interacting proactively with the applicant's team, the medical writer's goal should be to ensure that the PIP application is as clear and focused as possible so that only a minimal number of issues for resolution are raised during its review by the PDCO.

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Author information

Douglas Fiebig started his career as a medical writer at Hoechst in 1996, after receiving his PhD in environmental microbiology and spending several years in academic research. After the company went through several mergers, culminating in the formation of Aventis, Douglas and two colleagues co-founded Trilogy Writing & Consulting in 2002. The focus of his work has been writing for regulatory submissions in all major pharmaceutical markets. Douglas has been involved in preparing Paediatric Investigation Plans (PIPs) since they became mandatory in 2007. He regularly runs workshops on the practicalities of writing PIPs for EMWA and other organizations, and currently serves in the EMWA Professional Development Committee.

Pharmacokinetics series
Children are not 'small adults'

For many years the therapeutic drug dose in children was determined by simply making a proportional adjustment of the adult dose based on the weight of the child relative to the adult. The view that children are just 'small adults' has been debunked by a greater understanding of physiological and biochemical ontogeny and the pharmacological differences that can occur in children compared with adults. Developmental changes in the 4 main pharmacokinetic (PK) processes, absorption distribution, metabolism and elimination (ADME) have been noted. For example changes with age in the absorptive surface areas such as the gastrointestinal tract, skin and lungs can influence the bioavailability of a drug. Generally clearance mechanisms in infancy and early childhood are inefficient. The drug metabolising enzyme cytochrome P450 1A2 (CYP1A2) is absent in neonates therefore they are unable to metabolise caffeine to paraxanthine. Adult levels are only reached after 1 year of age. CYP2C9 (which accounts for approximately 20% of oxidative drug metabolism) activity increases from birth to 10 years of age whereupon it exceeds that of an adult, thereafter there is a decline to adult levels. Renal function as measured by glomerular filtration rate develops with age. Adult values are generally reached by 1 year of age. Genetic variants of ADME genes, different disease phenotypes, disease progression, and concomitant treatment all contribute to this variation.

The paediatric population is far from homogenous, variability is potentially larger than that observed in the adult population. Based on organ maturation, body weight and body composition children can be classified into at least 4 different population categories; neonates (birth to 28 days), infants (28 days – 23 months), children (2–11) and adolescents (12 to 16/18 years old)[1]. The challenge for the drug developer is to understand the heterogeneity and how this affects the pharmacokinetic/pharmacodynamic relationship and ultimately the therapeutic dose; is it sufficiently different to that found in adults to warrant a dose adjustment?

Presently around 70% of the medicines given to the paediatric population and 93% of the medicines given to critically ill neonates remain unlicensed or are used off-label[2]. The regulatory authorities have taken steps to address this imbalance. The EMA state that for all new chemical entities innovators must consider a paediatric investigational plan (PIP). In some instances a waiver will be granted where the disease is not present in children, for example Parkinson's' disease. In all other cases a series of studies are required to investigate the quality, safety and efficacy of the drug in children to allow choice of the appropriate dosing regimens.

Estimating PK in children can be challenging, the mantra oft said is 'the need to do more with less'. Blood sampling for drug measurement is less extensive compared with adults (it's a volume issue!) and subjects tend to be fewer. This scenario lends itself to the use of population PK methodology[3]. Here data from all patients are analysed together and a mean set of population PK parameters (generally clearance and apparent volume of distribution) are estimated. The variability around these parameters can then be investigated in terms of the different age groups etc, within the paediatric population. A caveat with this technique is that to fully understand dose adjustment in each of these cohorts a sufficient number of patients needs to be investigated in each of the sub-groups of interest.

Understanding drug behaviour in children has great societal value. For new medicines it will result in the early licensing of innovative products for paediatric use. For existing drugs, the development of child appropriate formulations coupled with a greater understanding of the PK/PD relationships in children will increase the armamentarium of safe and effective medicines available to treat childhood disease.

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