Regulatory Writing

Developments in paediatric regulation

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Abstract

Recently, both sides of the Atlantic have seen developments in paediatric regulation. In Europe, the EMA has published a new template for the paediatric investigation plan (PIP), which should help dispel some (but by no means all) doubts and inconsistencies regarding the PIP document. In the USA, the Food and Drug Administration Safety and Innovations Act (FDASIA) has effectively made it mandatory to submit a paediatric study plan (PSP, the US equivalent of a PIP) soon after completion of phase II of development. Drug companies will need to work out how best to manage having two approved plans in parallel and avoid discrepancies.

Keywords: Paediatric investigation plan, PIP, Paediatric study plan, PSP

Those of you who have taken a recent EMWA workshop on paediatric investigation plans (PIPs) will be aware that it is not always easy to second guess what the Paediatric Development Committee (PDCO) – the EMA body responsible for reviewing the PIPs – is looking for. Briefly, for readers who are not familiar with paediatric regulation, a PIP is a document that a company prepares during clinical development of a new investigational medicinal product. It outlines the plan for development in children and the broad aim of this requirement is to ensure that appropriate paediatric studies are performed so that treating children with innovative products is no longer largely a matter of guesswork. An approved PIP (or a PIP waiver if the company does not believe that paediatric development is necessary or feasible) is mandatory for approval of a product in adults. After approval in adults, the PIP is checked for compliance, that is, whether the company has done what it said it would. Approval can be revoked in the event that the company has not complied with its obligations. In general, the company will try to limit the scope of the commitments as far as possible, particularly as it is hard to predict the exact direction of future clinical development and the company wants to avoid studies that add no value to their product.

The PIP guidance was sometimes contradictory as to the exact content and structure of the scientific part (i.e. Sections B–E), perhaps because the legislation was new and everyone was on a learning curve. The seemingly erratic header numbering, with a mixture of letters and Arabic and Roman numerals, did not help matters. Companies for the most part would be keen to produce compliant PIPs, but the way forward was not always clear.

European developments: New PIP template

Recently, some of the uncertainties would seem to have been cleared up with the publishing of a new PIP template on the EMA website in February.[1] The headings are largely equivalent to headings indicated under previous guidance. However, the new template provides the exact structure that the PDCO is expecting to see in the PIP document (it states on the EMA website that 'applicants are invited to use the preformatted template', which I think we can take as 'use this template'), as well as slightly more detailed guidance as to the sort of content that is expected under each heading.

One of the main novelties is the new 'key binding elements' forms. These outline what the applicant is actually committing to, and will be used to check compliance with the PIP during and after approval. Compared with the previous synopsis forms, these new forms contain less information, which is good from the companies' point of view. This will probably make PIP writing easier because the actual commitments will often be what generate most discussion within a team working on a PIP. That is not to say that the clinical strategy does not have to be carefully thought out and presented in the PIP document.

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Paediatric regulation in the USA

There have also been developments in paediatric regulations in the USA, with the Food and Drug Administration Safety and Innovations Act (FDASIA) being signed into law last year.[2] Part of the FDASIA included provisions for strengthening existing legislation on paediatric development (Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA)). Before, a paediatric study plan (PSP), the US equivalent of the PIP, could be submitted after the product had been approved in adults. Now, it must be submitted at the end of phase II development (within 60 days of the end-of-phase-II meeting), although it can be submitted earlier. This is more in line with the PIP, which should be submitted as early as possible (and preferably when adult pharmacokinetic data are available, that is, before phase II). The requirement for an early submission gives the agencies a much greater say in the paediatric development and can ensure that the paediatric programme is sufficiently detailed and, importantly, expedite paediatric approval and so reduce the window of off-label use in children (with the greater uncertainties about dosing, efficacy, or safety).

In addition to the different timing in the submission, there are other differences that are worth highlighting. First, the structure of the two documents is different (see Table 1). Although the PIP structure appears much more complex, if both documents adhere strictly to guidance, they should be of similar length (in the case of a PIP, the Q&A section on the EMA website suggests a maximum of 50 pages per condition, while a PSP should not exceed approximately 60 pages if the lengths for each section indicated in the template are observed[3]). Often, some of the material from one type of plan can be slotted into another; for example, material from Section B.1.1 of the PIP could be used in Section 1 of the PSP. Adaptation will often be necessary, however. The epidemiological data in particular will require a European focus for the PIP and a US focus for the PSP. In addition, the approach to waivers is somewhat different. In the case of a PIP, the grounds can be expected lack of efficacy and safety, disease not occurring in the target population (and this means almost literally zero cases, not just extremely low incidence or prevalence), and lack of significant therapeutic benefit. Like a PIP, a PSP waiver can also be granted for expected (i) lack of efficacy and/or

Table 1: Comparison of structure of paediatric investigation plan (PIP – EU) and paediatric study plan (PSP – USA)

PIP	PSP
Part B – Overall development of the medicinal product	***Part E – Applications for deferrals***
B.1. Discussion on similarities and differences and pharmacological rationale	1. Overview of the disease in the paediatric population
B.1.1. Similarities and differences of the disease/condition between populations	2. Overview of the drug or biological product
B.1.2. Pharmacological rationale and explanation	3. Overview of extrapolation to specific paediatric populations
B.2. Current methods of diagnosis, prevention, or treatment in paediatric populations	4. Request for product-specific waivers
B.3. Significant therapeutic benefit/fulfilment of therapeutic needs	5. Summary table of planned non-clinical and clinical studies
Part C – Applications for product-specific waivers	6. Paediatric formulation development
C.1. Overview of the waiver request(s)	7. Non-clinical studies
C.2. Grounds for a product-specific waiver	8. Addition data to support studies in children
C.2.1. Grounds based on lack of efficacy or safety	9. Clinical studies
C.2.2. Grounds based on the disease or condition not occurring in the specified paediatric subset(s)	9.1 Paediatric clinical studies
C.2.3. *Grounds based on lack of significant therapeutic benefit*	9.2 Clinical effectiveness and safety studies
Part D – PIP	10. Timeline of the paediatric development plan
D.1. Existing data and overall strategy proposed for the paediatric development	11. Plan to request deferral of paediatric studies
D.1.1. Paediatric investigation plan indication	12. Agreements for paediatric studies with other regulatory authorities
D.1.2. Selected paediatric subset(s)	
D.1.3. Information on the existing quality, non-clinical, and clinical data	
D.2. Quality aspects	
D.2.1. Strategy in relation to quality aspects	
D.2.2. Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development	
D.3. Non-clinical aspects	
D.3.1. Strategy in relation to non-clinical aspects	
D.3.2. Overall summary table of all planned and/or ongoing non-clinical studies	
D.3.3. Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies	
D.4. Clinical aspects	
D.4.1. Strategy in relation to clinical aspects	
D.4.2. Overall summary table of all planned and/or ongoing clinical studies	
D.4.3. Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies	
D.5. Timelines of measures in the PIP	

safety or (ii) lack of significant therapeutic benefit. In the case of a PSP however, the third category is 'necessary studies are impossible or highly impracticable (because for example, the number of patients is small…)'.[4] My reading of this is that epidemiological arguments of low patient numbers are more likely to be successful in a PSP. For particular age groups, the PSP can also include partial waivers based on difficulties developing an appropriate paediatric formulation. In the USA, if a waiver is granted on the grounds of expected lack of efficacy or safety, this must then be reflected explicitly in the product label.

New challenges

As a result of these new developments in the USA, regulatory affairs departments will now face the challenge of managing two paediatric plans with different timelines and somewhat different formats, while attempting to maintain an overall coherence in global paediatric development. This may be particularly problematic when the PIP and PSP review procedures overlap. The supposed greater dialogue between the EMA and the US FDA may in principle help limit diverging opinions, but differences will surely arise from time to time, given the different structures of the document and differences in the underlying legislation. The companies themselves will be keen to ensure that the commitments of the PIP and PSP are fully compatible to avoid further unnecessary burdens on the company. For the moment, both companies and agencies are still feeling their way.

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