Writing Pediatric Study Plans (PSPs) – The Impact of the Revised 2016 FDA Draft Guidance

An initial Pediatric Study Plan (iPSP) is an outline of the paediatric study or studies that the drug development sponsor plans to conduct in the US to confirm the suitability of drug usage in the paediatric population. Initial Pediatric Study Plans cover study objectives and design, age groups, relevant endpoints and the statistical approach.

Following iPSPs, amended PSPs (aPSPs) are prepared. The preparation of a Pediatric Study Plan (PSP) requires concise presentation of the information about the disease to be treated in children, along with all relevant current knowledge of the drug being developed, to build to a convincing rationale for the proposed PSPs. This article aims to address:

- the development of paediatric regulations in the US over time
- the definition, intent and timing of submission to the FDA, and types of PSPs
- the updated template requirements included in Appendix 1 of the 2016 revised FDA PSP guidance
- the need for, and contribution of professional medical writers in the development of PSPs
- a comparative overview of the essential differences and similarities between PSP (required in the US) and Paediatric Investigation Plan (PIP [required in the EU]) requirements

**Article**

Children make up approximately one-quarter of the world’s population, but despite this the majority of drugs used in children are usually prescribed ‘off-label’ and have not undergone rigorous testing within this population for safety and efficacy in well-controlled clinical trials. The historic lack of paediatric drug testing is due to a number of reasons including ethical issues, difficult trial design and recruitment issues, cost of paediatric studies, and lack of financial incentive for pharmaceutical companies. Another challenge is the diversity of the paediatric population; children of different ages (Table 1) have developmental (cognitive, physiological, and psychosocial) differences from adults, which make age- and developmental-related research of drugs important. Drugs that work in adults may not necessarily work in children, and simply reducing the adult dose to account for children’s reduced weight erroneously assumes proportional safety and efficacy.

"Kids aren’t just little adults. Drugs approved for adults may not fit kids’ needs”. Compared with adults, children absorb and eliminate the drugs from their bodies differently, can experience different side effects, and may require different drug formulations.

![Figure 1: The legal framework of paediatric regulations development in the US](image)

The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) are two key highlights of this development. The goal of both PREA and BPCA is to provide paediatric information in drug labelling to encourage the appropriate use of drugs in treating paediatric patients.

The 2003 PREA requested pharmaceutical companies to “assess the safety and effectiveness in pediatric patients” and to provide a mandatory iPSP whenever submitting a marketing application for a drug that includes a new indication, new active ingredient, new dosing form, new dosing regimen, or new route of administration (i.e. that is subject to the PREA). This applies to investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), and efficacy supplements. The intent of the iPSP is for pharmaceutical companies to identify paediatric studies early in clinical development and begin planning for these studies.

The overarching stated goals of the 2002 BPCA are:

1. to encourage the pharmaceutical industry to perform paediatric studies to improve labelling for patented drug products used in children, by granting an additional six-month patent exclusivity;
2. to encourage the National Institute of Health (NIH) to prioritise therapeutic areas, sponsor clinical trials, and other research about on- and off-patent drug products that need further studies in children.

“Before the BPCA and PREA became law, more than 80% of the drugs approved for use in adults were being prescribed for children but have not been tested on children; in 2013, this number had decreased to 50%.”

**Revised 2016 FDA Draft Guidance on PSPs**

In 2016, a new FDA draft guidance on PSPs was released, replacing the 2013 version. The 2016 version is a draft document and, as with all guidance documents (draft or final), it is non-binding for sponsors. It provides clarifications on old sections and includes a number of new sections:

- Section V.A. Materially Incomplete iPSPs
- Section VI. Relationship of Agreed iPSPs to the Requirement

<table>
<thead>
<tr>
<th>Paediatric category</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-term newborn infants</td>
<td>Pre-term</td>
</tr>
<tr>
<td>Term newborn infants</td>
<td>0 to 27 days</td>
</tr>
<tr>
<td>Infants and toddlers</td>
<td>28 days to 23 months</td>
</tr>
<tr>
<td>Children</td>
<td>2 to 11 years</td>
</tr>
<tr>
<td>Adolescents</td>
<td>12 to 16–18 years (a)</td>
</tr>
</tbody>
</table>

(a) Depending on region

**Table 1: Categorisation of paediatric population by age**
to Submit a Pediatric Plan with an Application
• Section VII. Contents and Timing of Requested Amendment to an iPSP
• Section VIII. Non-Agreed iPSPs
• Section IX. Reaching Agreement on the Non-Agreed iPSPs.

Initial PSPs (iPSPs)
An iPSP is an outline of the paediatric study or studies that the drug development sponsor plans to conduct in the USA to confirm the suitability of drug usage in the paediatric population, including to the extent practicable:
• study objectives and design
• age groups
• relevant endpoints
• statistical approach
• requests for a deferral, partial waiver, or waiver, as well as other information specified in the regulations promulgated by the FDA.

Appendix 1 of the Draft FDA guidance, i.e. the iPSP template that sponsors can easily download and use to develop iPSPs, has been updated to reflect these changes.

The Strategic Role of the Medical Writer in the Development of PSPs
Pediatric Study Plans are often complex, strategic documents that combine current and legacy knowledge of a drug and its place in the armamentarium. Although regulatory affairs managers may be well versed in paediatric regulations, it is the medical writer (with hands-on experience in preparing iPSPs) who can guide a team through the practical complexities of information selection and adequate presentation. This is crucial from early planning and inception right through to submission to the FDA. A professional medical writer helps submission teams better interpret and implement not only the data, but also the requirements of the revised guidance. The writer can suggest the best way to provide the health authority with the data they need in a format and presentation that is both succinct and clear.

An overview of the updated template requirements and of proposed key contributors by section is provided in Table 2.

<table>
<thead>
<tr>
<th>Section</th>
<th>Content (a)</th>
<th>Length (pages)</th>
<th>Key contributors/authors (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title page</td>
<td>The proprietary name and the established name of the drug, if any, for biological products, the proper name including any appropriate descriptors</td>
<td>1</td>
<td>Medical writer (MW); Regulatory affairs manager (RAM)</td>
</tr>
<tr>
<td>1</td>
<td>Overview of the disease in the pediatric population</td>
<td>1–3</td>
<td>MW, Clinical/medical director</td>
</tr>
<tr>
<td>2</td>
<td>Overview of the drug or biological product</td>
<td>1–3</td>
<td>MW, Clinical/ medical director</td>
</tr>
<tr>
<td>3</td>
<td>Overview of planned extrapolation or effectiveness to specific pediatric populations</td>
<td>1–3</td>
<td>MW, Clinical/medical director</td>
</tr>
<tr>
<td>4</td>
<td>Planned request for drug-specific waiver(s)</td>
<td>1–3</td>
<td>MW, RAM</td>
</tr>
<tr>
<td>5</td>
<td>Plan to request deferral of pediatric studies</td>
<td>1–3</td>
<td>MW, RAM</td>
</tr>
<tr>
<td>6</td>
<td>Tabular summary of planned non-clinical and preclinical studies</td>
<td>Not specified</td>
<td>MW, Chemistry, manufacturing, and controls (CMC) expert; Preclinical expert</td>
</tr>
<tr>
<td>7</td>
<td>Age-appropriate formulation development</td>
<td>1–3</td>
<td>MW, CMC expert</td>
</tr>
<tr>
<td>8</td>
<td>Non-clinical studies</td>
<td>1–3</td>
<td>CMC expert; MW</td>
</tr>
<tr>
<td>9</td>
<td>Clinical data to support design and/or initiation of studies in pediatric patients</td>
<td>1–5</td>
<td>MW, Clinical/medical director</td>
</tr>
<tr>
<td>10</td>
<td>Planned pediatric clinical studies</td>
<td>1–10</td>
<td>MW, Clinical/medical director; Pharmacologist; Statistician</td>
</tr>
<tr>
<td>10 1</td>
<td>Pediatric pharmacokinetic studies</td>
<td>1–10</td>
<td></td>
</tr>
<tr>
<td>10 2</td>
<td>Clinical effectiveness and safety studies</td>
<td>1–10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Timeline of the pediatric development plan</td>
<td>1</td>
<td>MW, Clinical/medical director</td>
</tr>
<tr>
<td>12</td>
<td>Agreement for pediatric studies with other regulatory authorities (c)</td>
<td>1–3</td>
<td>MW, RAM</td>
</tr>
</tbody>
</table>

(a) Source: Template in Appendix 1 of Revised 2016 FDA Draft Guidance (3).
(b) This list is a proposal driven by the content and expertise requirements of each section. Further contributors can be added, as deemed necessary and required by the standard operating procedures of a specific company.
(c) If there is a pending or agreed PIP with the EMA, sponsors should provide the corresponding application number (EMA-000206-PIP-01-08) (3). As good practice, sponsors should also consider letting the European Paediatric Committee (PDCO) know if a PSP is pending.
In terms of clinical studies to be conducted in certain age groups and indications in the paediatric population, companies can ask the FDA for one of the following options in an iPSP:

- **extrapolation**, whereby the applicant proposes to extrapolate efficacy (whenever possible, see requirements in Table 3) and safety results (in all cases) from the adult population to the paediatric population and provides a justification to support this approach;
- **deferral**, whereby paediatric clinical studies are proposed, but their completion and reporting are to be delayed until efficacy and safety have been demonstrated for the adult population;
- **waiver**, whereby the applicant proposes not to conduct paediatric studies; the waiver can be either full (no paediatric studies at all) or partial (no paediatric studies in certain paediatric age groups or certain indications)\(^3\).

Further details about situations when each of these options is applicable are provided in Table 3.

<table>
<thead>
<tr>
<th>Request</th>
<th>New drug (originator)(^3)</th>
<th>Biosimilars (filing under BLA)(^3,5,6,8)</th>
</tr>
</thead>
</table>
| Extrapolation | Only possible for efficacy, not for dosing or safety  
• from adult to paediatric population appropriate if the course of the disease and the effects of the drug are sufficiently similar in adults and paediatric patients  
• from one to another paediatric age group | If there is adequate paediatric information in the reference product labelling  
• if the applicant can show biosimilarity and provide a justification for the extrapolation to paediatric population  
• it is also possible to apply for extrapolation for some indications (a) and for either full or partial waivers for other indications or for specific age groups |
| Deferral | • if the drug or biological product is ready for approval for use in adults before paediatric studies are complete, paediatric studies should be delayed until additional safety or effectiveness data have been collected  
• if there is another appropriate reason for deferral | If there is no adequate paediatric information in the reference product labelling  
• if there is a deferral for the reference product |
| Full waiver | If the prerequisites for a full waiver are fulfilled and necessary studies are impossible or highly impracticable  
• there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all paediatric age groups  
• the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for paediatric patients and is not likely to be used in a substantial number of paediatric patients | If there is no adequate paediatric information in the reference product labelling  
• if there is a waiver for the reference product and the applicant believes that the proposed product meets the requirements for a waiver  
• it is also possible to get a full waiver for some indications (age groups) and a partial waiver for others |
| Partial waiver | If a partial waiver is sought, the following applies in addition to the requirements described above for a full waiver  
• if the sponsor can demonstrate that reasonable attempts to produce a paediatric formulation necessary for that age group have failed | See above under “Extrapolation” and “Full waiver” |

\(^3\) A proposed biosimilar will obtain approval in all indications where the original biologic is approved once shown to be biosimilar; a biosimilar development programme is thus only provided.

### Table 3: Options for addressing the PREA through the iPSP

Once the initial iPSP has been submitted, the clock starts ticking, and pharmaceutical companies should be prepared to deal with very tight timelines. A professional medical writer can support a project team throughout this process, driving the document forward, aligning strategies and review comments, and helping teams to anticipate and prepare for potential questions that the FDA might provide.

An overview of the required timing for submitting an iPSP is given in Table 4.

| General guidance\(^3\) | 60 days after the end-of-Phase II (ROPs) meeting and/or before the initiation of Phase III studies.  
No later than 210 calendar days before a marketing application is submitted to allow for an iPSP agreement prior to the marketing application. |
|------------------------|--------------------------------------------------------------------------------------------------|
| Biosimilars-specific\(^6\) | FDA recommends not later than 210 days before initiating a comparative clinical study (if not already initiated).  
Depending on the details of the clinical programme, it may be appropriate to submit an iPSP earlier in the development. |

### Table 4: Timing of iPSP submission

Upon FDA feedback, an experienced medical writer can help to sculpt crisp key messages, free of ambiguity, to address any regulatory concerns. Additionally, the medical writer can make sure that the technical requirements of the new iPSP version are met in a timely manner. The steps from iPSP submission to iPSP agreement are presented in Table 5.

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Clock stop (Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission of the iPSP to the FDA by the sponsor</td>
<td>0</td>
</tr>
<tr>
<td>FDA provides comments on the iPSP</td>
<td>90</td>
</tr>
<tr>
<td>Submission of the iPSP to the FDA by the sponsor (with FDA feedback incorporated)</td>
<td>180</td>
</tr>
<tr>
<td>FDA provides final agreement with the iPSP (or a letter stating that the iPSP isn’t agreed)</td>
<td>210</td>
</tr>
</tbody>
</table>

### Table 5: Steps from iPSP submission to iPSP agreement (or disagreement)\(^6\)

An iPSP that fails to include the required information is deemed materially incomplete by FDA. If this applies, the FDA will contact the sponsor, who has 30 days to address insufficiencies. Thus, proper planning of timelines and resources is needed to ensure that all required functional roles are available to address any deficiencies that might be identified. Hence, it is of utmost importance that sponsors 1) have a clear understanding of the FDA requirements...
and their options of addressing the PREA before starting to plan for paediatric studies; and 2) plan ahead and refine their iPSP strategy well in advance of the EOP2 meeting. Once the sponsor submits an updated iPSP, a new 210-day review period starts.

**Amended PSPs (aPSPs)**

There are several situations in which the sponsor may wish to amend the iPSP, or a previously aPSP:

- changes to an original milestone submission date that would significantly delay the initiation and/or completion of paediatric studies, e.g. more than 12 months;
- changing planned requests for a deferral to planned requests for a partial waiver;
- changing a planned request for a (partial) waiver to planned requests for a deferral.

The sponsor may amend an agreed iPSP at any time. However, if the aPSP is submitted within 210 days of a planned NDA/BLA submission or supplement, the amendment may not be considered to be agreed by the FDA, because the FDA will not have sufficient time to review it. The NDA/BLA or supplement can be submitted if the previously agreed iPSP is included in the submission package, in this case, any changes will be considered during the application review cycle. If the agreed iPSP included paediatric studies that the sponsor failed to complete, this will result in a failure to file.

While it may be tempting for authoring teams used to writing PIPs to think that PIPs and PSPs are quite similar in terms of content and procedural requirements, they also differ significantly. While both the PIP and PSP are generally mandatory documents for new drug applications, a number of differences must be considered in detail. See Table 6 for further information.

<table>
<thead>
<tr>
<th>Region</th>
<th>Law/regulation</th>
<th>Aim</th>
<th>Differences</th>
<th>Similarities</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/EMEA</td>
<td>Regulation (EC) No 1901/2006 (a)</td>
<td>Assess safety and efficacy/effectiveness of new drugs/biologics in paediatric patients</td>
<td>Time</td>
<td>New drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biologics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biosimilars</td>
<td>Extrapolation, waiver (full or partial), deferral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Review and decision</td>
<td>Length of document</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EMA decision</td>
<td>Six-months’ additional protection/patent exclusivity (c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paediatric Committee (PDCO) Opinion</td>
<td>Incentives</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FDA decision</td>
<td>Six-month Supplementary Protection Certificate extension under the BPCA in the US</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pediatric Review Committee</td>
<td></td>
</tr>
</tbody>
</table>

(a) According to the Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, the requirement to submit a PIP “should not apply to generics or similar biological medicinal products.”

(b) According to the PREA and the revised 2016 FDA draft guidance on PSPs, “a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new active ingredient for purposes of PREA’s.” If no Phase II or III studies are planned for a biosimilar product, the applicant may request a PSP waiver.

(c) Additional six-month patent exclusivity under the BPCA in the US.

In summary, the intent of the PSP – as defined by the revised 2016 FDA draft guidance – is for pharmaceutical companies to...
identify paediatric studies early in the development and begin planning for these studies, in order to ensure increased effectiveness and safety in the paediatric population. An iPSP is an outline of the paediatric study or studies that the sponsor plans to conduct in the US – to confirm the suitability of drug usage in the paediatric population. Initial PSPs cover study objectives and design, age groups, relevant endpoints, and statistical approach. Amended PSPs are prepared, as necessary, after iPSPs have been produced.

The revised 2016 FDA draft guidance and its updated template demand that sponsors follow a leaner and more targeted approach in developing their iPSPs. The preparation of a PSP requires concise presentation of information about the disease to be treated in children, as well as a description of all the relevant current knowledge of the drug being developed, placing this and the latest data into context and in doing so allowing a convincing rationale for the proposed PSP to be put forward. Medical writers can use their specialist knowledge in helping companies not only to understand the proposed PSP to be put forward. Medical writers can use their specialist knowledge in helping companies not only to understand the proposed PSP but also to deliver appropriate PSP messages in a concise, targeted, and timely manner, thereby contributing to a successful IND, NDA, BLA, or efficacy supplement submission in the US.

REFERENCE


Diana Radovan, PhD

Diana Radovan PhD is a Senior Medical Writer at Trilogy Writing & Consulting GmbH. After obtaining an MSc degree in Biochemistry and Molecular Biology in Bremen, Germany and a PhD degree in Biophysical Chemistry as graduate student of the International Max Planck Research School for Chemical and Molecular Biology in Dortmund, Germany, she was a postdoctoral fellow at the Health Research Innovation Centre of the Faculty of Medicine, University of Calgary, Alberta, Canada. During her postdoctoral training, she was a Canadian Science Writers Association and Genome Alberta scholar and received intensive training on communicating science to the general public through the immersive Banff Science Communications programme. In her previous medical writing roles at Boehringer Ingelheim GmbH & Co. KG and Hexal AG, Sandoz Biosimilars, a Novartis Division, she worked on a broad spectrum of regulatory documents and therapeutic indications as a lead writer, she gained both originator and biosimilar experience and hosted trainings on best practices for writing and reviewing regulatory documents, including PSPs. She holds an Advanced Certificate in Medical Writing from the European Association of Medical Writers (EMWA) and is a supporting member of EMWA’s Pharmacovigilance Special Interest Group.

Email: diana.radovan@trilogywriting.com

Rachel Beeby, MSc

Rachel Beeby MSc is a Medical Writer at Trilogy Writing & Consulting UK Ltd. Following her undergraduate studies in Physiotherapy and Medical Sciences at Manchester Universities, UK, she re-focused her career on science, completing her MSc degree in Molecular Medicine at the University of East Anglia. Before joining Trilogy, Rachel was a medical writer at Micron Research Ltd, a CRO with specialist interest in infectious disease. Here, she worked on publications including manuscripts, abstracts, and posters. Since joining Trilogy, Rachel has been developing her experience on regulatory documents.

Email: rachel.beeby@trilogywriting.com