How to Successfully Prepare for Your Pediatric Study Plan

Laws were implemented surrounding the safety and efficacy of drugs and biologics starting in the early 1900s, however, the inclusion of pediatric use in drug labeling has significantly lagged behind. Many factors led to this lack of pediatric information including ethical, monetary, and feasibility challenges. The lack of data for pediatric use leaves physicians with only empirical and experiential methods to dose children, leading to increased risks in this population.

The Food and Drug Administration (FDA) began increasing efforts to ensure that pediatric use information was provided in all drug labels in 1994. The FDA first published a rule that required manufacturers to determine whether existing data were sufficient to update drug labels for pediatric use. Unfortunately, this rule did not lead to substantial changes in labeling as it did not require any studies to be conducted if current data did not support pediatric use.

The FDA Modernization Act of 1997 and the Pediatric Rule of 1998 implemented additional incentives and requirements for the conduct of pediatric studies. Legal battles, however, led to the Pediatric Rule being overturned in 2002.

Congress granted FDA the authority to regulate pediatric studies in 2003 with its passage of the Pediatric Research Equity Act (PREA). Under PREA, all Sponsors are required to conduct studies to assess the safety and effectiveness of their products in pediatric populations. The FDA Safety and Innovation Act (FDASIA) of 2012 implemented requirements for all Sponsors to include a proposed timeline and design of pediatric studies during the investigational new drug (IND) stage. This plan is known as an initial pediatric study plan (iPSP).

Initial Pediatric Study Plan

An iPSP is required for all Sponsors that plan on submitting a marketing application (NDA or BLA) for a drug that includes a new:

- Active ingredient
- Indication
- Dosage form
- Dosing regimen
- Route of administration

One exception is if the drug or biologic has been granted orphan designation for the proposed indication at the time the iPSP is required (see Orphan Designation below).

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Planning and Timeline for an iPSP Submission

FDA agreement on an iPSP is required prior to the submission of a marketing application or supplement. It is important to note that failure to include an agreed iPSP in a marketing application that is subject to PREA may be grounds for a refuse-to-file action.

Per FDA guidance, the submission of an iPSP should occur no later than 60 days following the end of phase 2 (EOP2) meeting. Ideally, the iPSP should be drafted after EOP2 studies are completed but prior to the EOP2 meeting. This will allow for discussions around endpoint considerations for both the adult and pediatric studies at the EOP2 meeting. If the initial plans for an IND include only a phase 3 study, the iPSP should be submitted as a pre-IND submission. In this case, it is strongly recommended that Sponsors schedule a pre-IND meeting prior to the submission of an iPSP.

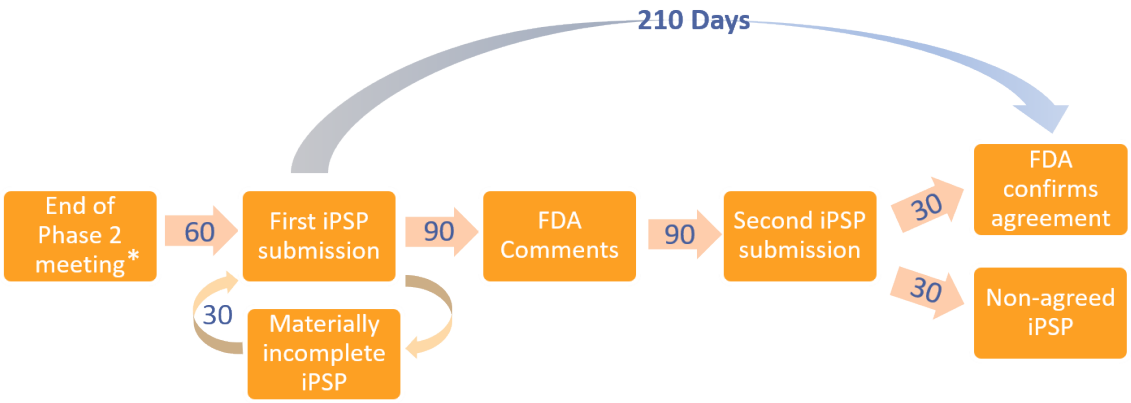
Timelines associated with an iPSP are long. When considering timelines for your program, budget in at least two months to draft an iPSP. The FDA guidance titled, "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans," outlines the expected contents for an iPSP. Sponsors should make sure that all functional areas are available for input including toxicology, manufacturing, clinical, pharmacokinetics, and pharmacometrics. The total review period with the FDA is 210 days. Below is an image that outlines the iPSP submission process for the FDA:

Any issues with a submission, such as a materially incomplete iPSP or non-agreed upon iPSP, will add weeks to months to this timeline. Subsequent reviews of non-agreed iPSPs lack any statutory timeline requirements, so it is important to ensure that the first iPSP versions are well thought out and as complete as possible. Even though the FDA may agree to an iPSP, it is not formally approved until the marketing application is submitted.

Orphan Designation

Orphan designation applies to drugs or biologics that are intended for the treatment, prevention, or diagnosis of a disease or condition that affects less than 200,000 people in the United States. According to the Pediatric Study Plan guidance, Sponsors are exempt from submitting an iPSP if their drug or biologic has been granted orphan designation for the proposed indication at the time the iPSP is required. However, some exceptions now apply.

On August 18, 2017, the RACE for Children Act was incorporated as Title V of the 2017 FDA Reauthorization Act (FDARA) to amend PREA. According to this act, all new drugs and biologics that are "intended for the treatment of adult cancers and are directed at a molecular target substantially relevant to the growth and progression of a pediatric cancer" are required to conduct pediatric studies, regardless of orphan status.



* If no EoP2 meeting, iPSP should be submitted before initiation of P3 (or combined P2/P3) studies.
** If no P3 or P2/P3 studies, no later than 210 days before marketing application submission.
*** If no active IND and initial studies will be P3, iPSP is pre-IND submission.

To assist in determining whether a drug or biologic will be affected by this regulation, the FDA's Pediatric Oncology Program has released a Pediatric Molecular Target List which differentiates targets based on their relevance to the growth or progression of pediatric cancers. This rule applies to any new applications with planned submission dates after August 18, 2020.

Extrapolating Efficacy from Adult to Pediatric Populations

Plans for full or partial extrapolation of efficacy from adult to pediatric populations or from one pediatric population to another should be included in an iPSP. Prior to discussing extrapolation, it is key to provide a clear description of the similarities and differences between adults and pediatric populations that pertains to the drug, indication, epidemiology, and the unmet medical need. If the disease and effects of a drug are sufficiently similar between adults and pediatrics, it may be possible to fully extrapolate efficacy. The majority of iPSPs include plans for partial extrapolation of efficacy (with differences in dosing).

If the ability to extrapolate effectiveness from adults to children is not known or is not present, the iPSP must include plans to establish effectiveness with at least one placebo-controlled trial. More often than not, Sponsors will be required to run a small study to gain safety information even if they can demonstrate similar efficacy across populations. In almost all cases, safety cannot be extrapolated from adults, but safety data can be leveraged (particularly if the mechanism is well known and there is an exposure-response relationship).

One of the goals within the extrapolation section is to discuss how pediatric subjects will be dosed. The pediatric dose is typically determined based on modeling and simulation. It is important to note that modeling and simulation results do not necessarily need to be included in the iPSP. It is acceptable to include only the plans for these analyses as the dosing and study design will not be approved until the Agency reviews the actual protocol.

iPSP Waivers and Deferrals

The waivers section of the iPSP is where companies can request a waiver or, more likely, a partial waiver for studying certain age groups if any of the following criteria are met:

- Necessary studies are impossible or highly impracticable
- There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in pediatric age groups
- The drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients
- The drug or biological is not likely to be used in a substantial number of pediatric patients
- Reasonable attempts to produce a pediatric formulation necessary for that age group(s) have failed

The waiver section should provide justification with a summary of supporting data from all available sources (e.g., Sponsor data, published literature, expert panels, workshops) for all age groups for which the waiver will be sought. Full or partial waivers previously granted for other drugs in the same class can be considered supportive information.

Sponsors submitting a plan for a full waiver of pediatric studies still need to submit an iPSP on the standard timeline with Sections 1, 2, 4, and 12 included. The deferral section of the iPSP is where companies request deferrals of pediatric assessments in some or all pediatric groups until after marketing approval or until data from ongoing or planned studies are complete.

It is important to note that waivers and deferrals are not formally granted with the response to the iPSP. Instead, the FDA formally grants waivers and deferrals when it issues an approval letter for the marketing application. If a waiver request is based on an indication that appears on the list of adult-related conditions that rarely or never occur in children, a one-page plan that specifies the drug product is intended for the treatment of such a condition and a statement of plans to request a full waiver of pediatric studies is sufficient.

Remaining Sections of the iPSP

The remaining sections of the iPSP describe results from completed pre-clinical and clinical studies, study designs of planned and ongoing pre-clinical and clinical studies, and the timelines for conducting these studies.

The other key feature described in the iPSP is planned pediatric formulation(s). It is important to plan ahead for pediatric formulations (e.g., dispersible tablets, suspensions) because the formulation could be the rate-limiting step to conducting pediatric studies. Typically, when a new pediatric formulation is planned, a relative bioavailability study will be conducted in adults first.

While the formulation does not have to be bioequivalent to the adult formulation, there is a need for the pediatric dose to be adjusted based on body weight (or age) and the difference in relative bioavailability, if there is one. If the relative bioavailability of the pediatric formulation is very low compared to the adult formulation, then multiple tablets must be administered to pediatric patients, creating a feasibility issue.

Amended PSP (aPSP)

A Sponsor can request an amendment at any time. Some examples for reasons to amend a PSP include:

- Changing a date in Section 11 that would significantly delay the initiation or completion of pediatric studies (e.g., by more than 12 months)
- Changing planned request for a deferral to planned request for a waiver or partial waiver
- Changing a planned request for a waiver or partial waiver to a planned request for a deferral

The timeline for an amendment is the same as an iPSP. If the request is submitted within 210 days of the planned submission of an NDA, BLA, or supplement, the amendment may not be considered agreed at the time of filing. Failure to complete nonclinical or pediatric clinical studies that were expected to have been completed before submission of the marketing application may result in a refuse to file. Requests for amendments do not need to be submitting after acceptance for filing an application or supplemental application.

Other Important Considerations

- All pediatric age groups need to be addressed in an iPSP
- The submission of an iPSP is required even if a drug or biologic is being developed for use in pediatric populations
- A new iPSP needs to be submitted even if a new application is being submitted for a drug or biologic that was previously approved or was granted a waiver or deferral under PREA
- iPSPs are required for biosimilars that are not considered interchangeable with the reference product

Conclusions

The FDA guidance for Pediatric Study Plans is a great place to start as it provides clear expectations for the submission and preparation of iPSPs; however, it can still be challenging to write and reach an agreement with the Agency.

Although the regulations surrounding pediatric studies have been around for years, the submission of an iPSP can still catch many Sponsors off-guard when preparing for their marketing applications or heading to their EOP2 meetings. An agreed iPSP or amended PSP is ultimately critical for a successful marketing filing and approval.

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