

RACE for Children Act: Product Development Considerations

With new regulations such as the RACE for Children Act coming into play, it is important to address the requirements for paediatric drug developers going forwards

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In August 2020, the RACE for Children Act will go into effect. Until now, certain treatments, such as cancer drugs with orphan designation, were exempt under the Pediatric Research Equity Act (PREA). The RACE for Children Act eliminates the orphan exemption for new cancer drugs directed at molecular targets relevant to children's cancers.

Complying with the RACE for Children Act and PREA

With the RACE for Children Act, any *original* new drug application (NDA) or biologics licence application (BLA) submitted on or after 18 August 2020, for a new active ingredient to treat an adult cancer indication with orphan designation, must have an agreed paediatric study plan (PSP) in place (even if the adult indication does not occur in children) if the molecular target is substantially relevant to the growth or progression of a paediatric cancer. More drug developers will now need to consider the implications of PREA. In December 2019, the FDA issued a draft guidance to help companies comply with the new regulations (1).

As a requirement of the statute, the FDA published, in August 2018, a list of relevant paediatric molecular targets "for which existing evidence

and/or biologic rationale exist to determine their potential relevance to the growth or progression of one or more pediatric cancers" (2). Currently, over 200 possible targets have been identified on this list, which is being updated continually as new information becomes available. It has also developed a list of "non-relevant pediatric targets that warrant waiver from the pediatric requirements".

For those relevant paediatric targets, PREA mandates that sponsors who plan to market their drug in the US have an agreed PSP in place at the time of filing, and it is important to start now, anticipating at least three to four months for plan development and another seven months to reach agreement with the FDA.

Here are some of the key PREA considerations:

- Unless otherwise exempt, sponsors planning to submit a marketing application for a new active ingredient, indication, dosage form, dosing regimen, or route of administration are subject to PREA
- A biosimilar is considered a 'new active ingredient' and is subject to PREA
- All paediatric populations (from birth up to less than 17 years of age)

must be addressed in the plan; even products not developed for use in adults are subject to PREA

- PREA requires that a PSP must be submitted to the FDA within 60 days after the end-of-Phase-II (EOP2) meeting. In cases where an EOP2 meeting is not held, the PSP should be submitted before Phase III or combined Phase II/III studies are initiated. In any event, the plan should be submitted at least 210 days before submission of the marketing application to be sure an agreed plan is in place at the time of filing; not having a plan in place for a product subject to PREA may be grounds for a refusal to file
- Waivers from conducting paediatric assessments in some (partial) or all (full) can be granted under certain conditions:
 - If studies are impossible or highly impracticable
 - If strong evidence exists to suggest that the treatment would be ineffective or unsafe
 - If the drug 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 it is not possible to develop an age-appropriate paediatric formulation



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Key Considerations for Drug Developers

Drug developers and researchers looking to develop cancer therapies need to be prepared and should consider the following.

Consider the List of Targets and Perceived Waivers

The list of targets and perceived waivers should be considered early and frequently as they may change. This list of relevant targets from the FDA fulfils the organisation's statutory requirements from FDARA (FDA Reauthorisation Act of 2017). It is expected to provide guidance to industry in planning for initial PSP submissions for new drug and/or biologic products in development for cancer, in accordance with the

amended provisions of the RACE for Children Act. However, it is important to note that this list should be considered a guide and will likely change as new targets are developed.

Don't Assume an Automatic Waiver

Even if the molecular target being researched is one of the few present on the waivers list, the FDA must still approve the waiver, and the sponsor will need to file a plan. A waiver is not necessarily automatic, and the waiver list may change as more is known. When in doubt, request a meeting with the FDA ("Request for FDARA iPSP Meeting").

Recognise that Paediatric Trials have Different Requirements

Paediatric trials have different requirements than those for adults

and may require new skill sets and ways of doing things. Drug developers new to paediatric trials will quickly discover distinctions surrounding participation, consent/assent, trial design, and other factors. Additionally, unlike some other therapeutic areas, results from oncology clinical trials cannot simply be extrapolated from adults to children. Instead, paediatric kinetics must be evaluated. Early identification of the need to do paediatric clinical trials and planning can be essential to good design and implementation.

Take a Global Approach

Paediatric cancers are rare. Therefore, to effectively and efficiently meet the enrolment objectives of paediatric studies, a global approach must be undertaken. Now more than ever, drug developers intending to market their

drug in the US and EU will need to think strategically about aligning paediatric clinical development plans to meet the demands of the FDA and EMA.

Assess Timelines from Different Perspectives

Almost all sponsors will need to file a paediatric plan. In the US, the PSP should be submitted after completion of Phase II. If not enough information is available, permission for a deferral can sometimes be obtained (3). To market a drug in Europe, a paediatric investigative plan (PIP) will need to be filed with the EMA (4).

Gain a Sense of the Bigger Picture

The RACE for Children Act offers insights into longer-term implications of paediatric regulations as well as indications of where science and the industry are headed. Collaboration among regulatory agencies is on the rise, increasing the compatibility of requirements when it comes to paediatric drug development.

Work with an Expert

According to the Coalition Against Childhood Cancer, only 11 drugs already approved in adults had been approved for use in children with cancer from 1980 to 2017. Many sponsors will have limited paediatric drug development experience. It is important to start conversations early and often with a CRO who is experienced not only in the conduct of oncology trials, but with extensive paediatric drug development expertise. A good partner will draw on extensive experience in this space to suggest efficiencies: see following.

Assessing Trial Options

It may be suggested to assess the trial options that address multiple, child-relevant indications simultaneously with innovative trial designs.

Considering New Approaches

New approaches may be considered that are more flexible, such as adaptive trial capabilities to leverage results as they accumulate in the trial to modify the course as needed, according to pre-specified rules.

Quantitative Clinical Pharmacology Modelling and Simulation

Both the FDA and EMA recognise the role of pharmacokinetics (PK) in paediatric drug development. For instance, modelling and simulation can help inform the safe starting dose, optimal dose regimen, and optimisation of the study design – including PK sampling strategy.

Considering Practical Approaches

A good partner in paediatrics will think outside the box. They can often assess things such as the burden of protocol on children or families, what children can and cannot tolerate (with blood draws, tests, etc.), ways to minimise resistance to study participation, and more.

Consent Requirements and Effective Communication

In the US, most institutional review boards consider that a child as young as seven years of age can provide assent. In some European countries, a child as young as three years of age will be expected to provide assent. A good CRO should be able to advise on how to best communicate with children of various age groups, and with parents. Communicating effectively on things such as study requirements (e.g., procedures), time commitments, risks, and potential benefits of study participation will enhance study recruitment and retention.

Gaining a Multidisciplinary View

With CRO project teams able to collectively assess various aspects (and lessons learnt) across disciplines, they can often increase the likelihood of trials being completed on time and on budget.

Assessing Opportunities

Drug developers may be able to take advantage of opportunities such as Congress re-authorising, through 2020, the Rare Pediatric Disease Priority Review Voucher programme in the 21st Century Cures Act to provide incentives to address unmet medical needs for children and other patients with rare diseases. Drug companies that receive approval for a treatment for a rare

paediatric disease may qualify for a voucher for priority review of a future marketing application for a different product. A good partner will likely be able to assess these and other potential opportunities, in addition to expanding on capabilities and expertise.

Final Thoughts

With increasing regulatory requirements, paediatric development is no longer an add-on to drug development. Instead, paediatric research should be integrated early in the overall product development plan. The intended result is more treatments for children who need them.

References

1. Visit: www.fda.gov/media/133440/download
2. Visit: www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
3. Visit: www.fda.gov/files/drugs/published/Guidance-for-Industry-%28Draft%29--How-to-Comply-with-the-Pediatric-Research-Equity-Act--%28posted-9-7-2005%29.pdf
4. Visit: www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/paediatric-investigation-plans-questions-answers#1.-applying-for-a-pip,-waiver-or-deferral-section



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