Closing the Gap in Pediatric Oncology Drug Development: The Regulatory Landscape and the RACE for Children Act

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Pediatric approvals of oncology treatments over the last 20 years have brought new hope to patients, especially as anticancer drug development has focused on biologically targeted therapies. But the pediatric cancer treatment landscape still struggles with a lack of approved options for several pediatric cancer types.

The current regulatory environment can help support sponsors with the complex efforts involved in pediatric oncology drug development, as regulatory agencies and legislative acts have helped encourage, incentivize or even require the conduct of pediatric trials in other indications. This white paper provides a brief history of how pediatric cancer treatments have progressed, outlines how regulatory changes have impacted the field of pediatric drug development and provides guidance on applying current regulations, such as the RACE for Children Act, which is focused on pediatric oncology. This change should serve to enhance an inclusive regulatory strategy for oncologic drug development.

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Evolving Regulations for Pediatric Drug Development

Pediatric cancers are considered rare diseases, which are defined in the U.S. as diseases that affect fewer than 200,000 people. Many pediatric cancers still have limited treatment options, a problem exacerbated by the limited incentives and regulations for companies to develop therapeutics targeted against pediatric cancers.

Drugs are often used in children "off label," without the same level of evidence that has been obtained in adults. Conducting pediatric trials is inherently more complex than running trials in an adult population and pediatric cancer is especially complicated as the cancer types commonly observed in children are largely different from adult cancers; even the same type of tumor can behave differently in children.

In one of the first notable attempts to improve pediatric drug development, two significant regulatory "game-changers" were introduced in the 2000s in the U.S. with the Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA), both of which built off of legislation passed in the late 1990s.

- BPCA (2002) was part of the reauthorization of the 1997 FDA Modernization Act (FDAMA), maintaining a six-month exclusivity added to patent life of the active moiety for sponsors who voluntarily completed pediatric clinical studies; it also created the Office of Pediatric Therapeutics (including ethicist) and a mandate for pediatric-focused safety reviews[1]
- PREA (2003) reestablished many components of the FDA's 1998 pediatric rule; orphan products are exempted
- Both BPCA and PREA were made permanent by FDASIA (FDS Safety and Innovation Act) in 2012

While PREA and BCPA resulted in more approvals and label changes for pediatric use, an average lag time of eight years still exists between approval of the original adult indication to the addition of pediatric-specific labeling.[2] Even today, only about 20% of approved drugs in the market are appropriately labeled for pediatric use. Likewise, only a small portion of the commonly used drugs in neonatal intensive care unit (NICUs) are FDA approved,[3] stressing the ongoing need for additional scientific investment.

According to data from the Center for Drug Evaluation and Research (CDER), waivers and deferrals remained about the same and, in some years, even increased between 2012-2018, despite the legislative changes of PREA and BPCA. Furthermore, there were just over 25 approvals and labeling updates associated with pediatric cancer drugs in the last decade, which represents only a fraction of changes compared to other therapeutic areas.

Given the noticeable lack of therapies for the pediatric population, additional legislation was needed to "close the loophole" of the orphan exemption and ensure greater development of cancer drugs for children.

Urgent Unmet Needs in Pediatric Oncology

Conditions that don't have good response or available therapies include:

- Sarcoma and renal cancer
- Rhabdomyosarcoma, Ewing sarcoma, renal tumors
- Neuroblastoma
- Osteosarcoma
- Leukemia/lymphoma
  - Relapsed lymphoid leukemia, acute myeloid leukemia
- Brain tumors
  - Medulloblastoma, ependymoma, high-grade gliomas

Introducing the Research to Accelerate Cures and Equity (RACE) for Children Act

With improved knowledge of tumor biology, the research community has exponentially increased the development of targeted therapies to create "precision medicines" that align to a patient's genomic profile. If one of these novel precision medicines is directed at a molecular target in an adult cancer, and the FDA determines this target to be "substantially relevant to the growth or progression of a pediatric cancer," then a pediatric investigation can be required per the Research to Accelerate Cures and Equity (RACE) for Children Act.

The RACE for Children Act amends PREA as part of the 2017 FDA Reauthorization Act (FDARA), with the goal of promoting research and development of new cancer treatments for children. It was enacted in 2017 and will be enforced starting August 2020.

With the RACE for Children Act, drugs designated as orphan are no longer exempt from PREA and waivers are limited for pediatric assessments of medications that target a molecule germane to a pediatric cancer for which there is a need for additional treatment options. The FDA has published an evolving document, the Pediatric Molecular Target List, which includes more than 200 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, and those targets for which there is evidence that they are not associated with pediatric tumors for which pediatric studies would be waived,"[4] but the information in the list is subject to change.

Sponsors may be incentivized to develop drugs for pediatric rare disease with a pediatric priority review voucher as part of the Rare Pediatric Disease Priority Review Voucher Program within the Creating Hope Act, which was first passed in 2012 and reauthorized several times. In this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. Trading at $100 million to $350 million, these vouchers are creating a significant incentive for pediatric rare disease drug development.

Pediatric patients have also benefited from the program. Since the enactment of the Creating Hope Act, 19 new drugs for children with life-threatening illnesses have been approved, including two for childhood cancers.[5] As part of the 21st Century Cures Act enacted in 2016, it is scheduled to sunset in 2020, but there's hope that it will be extended. Regardless, drugs that are approved by 2022 will be eligible.

The RACE for Children Act and Implications for Pediatric Drug Development

With the RACE for Children Act, discussions about pediatric studies and pediatric development may occur earlier for U.S. development. Finding the most appropriate development plan for a pediatric oncology product involves conducting early evaluation of molecules, including proactive preclinical testing, in order to advance or disprove the need for clinical studies in children with cancer. When conducting pediatric studies, sponsors need to plan in advance of the study to determine:

- If preclinical data are needed, the timing of the studies
- How to develop a pediatric formulation (if needed)
- The starting dose and dose regimens
- The expected variability between adults and children and how much data can be extrapolated from adult studies
- Appropriate endpoints and biomarkers

Depending on the specific molecular targets, early regulatory engagement, starting as soon as pre-IND meetings, is key to navigating new regulations surrounding pediatric treatments. Sponsors should also consider that smaller study populations will require the development of innovative study designs, such as adaptive designs or the inclusion of real-world evidence or historical controls. Current pediatric studies face recruitment challenges due to the relative numbers of affected children to the population as a whole, just as other trials in rare disease indications. Collaborations are also key for development, and sponsors should consider forming relationships with advocacy groups, the National Cancer Institute, academia and cooperative treatment consortia.

A Global Outlook for Cancer Therapies in Children

Outside of the U.S., the EU also has mandatory pediatric drug development regulations with a Pediatric Investigation Plan required (PIP) before Phase II. Both the U.S. and EU require pediatric plans to be addressed, whether through a plan deferral or waiver.

While the EU and the U.S. have similar pediatric legislation, they are not completely harmonized. The FDA looks at indications, while the European Medicines Agency (EMA) looks at conditions, and extrapolates to similar population subsets and disease subtypes or stages, among others. With the RACE for Children Act and targeted agents, there may be more harmonization based on the mechanism of action of the therapy but approval from one regulatory body does not guarantee approval from the other.

On a global level, a longstanding partnership between a number of national regulatory bodies (FDA, EMA, etc.), called the Pediatric Cluster, exists with the aim to enhance the science of pediatric trials, and to harmonize regulatory requirements where possible to avoid exposing children to unnecessary trials. Starting in 2007, EMA and FDA established monthly teleconferences between regulators to discuss product-specific pediatric development and topics related to product classes under the terms of confidentiality agreement.

The Pediatric Cluster also includes Japan's PMDA (which does not have mandatory pediatric development but it is encouraged), Health Canada and Australia's Therapeutic Goods Administration (TGA).

Considering Scientific and Operational Perspectives

Given that the molecular mutational landscape and genomic architectures for pediatric tumors are different than those for adults, sponsors must consider the interrelationship between pharmacokinetics (PK), pharmacodynamics (PD) and pharmacogenetics (PG). PK, PD and PG all are subject to a wide range of developmental changes seen in children, and play a role in an individual's phenotype and their clinical outcome. Biodisposition can be thought of as pieces of a PG/PK/PD puzzle, uniting disease-specific PD data for children, safety/tolerance data, acceptable formulations, PG and age-relevant PK data. Together, these parameters can help to provide for rational drug development in children.

As children undergo physiological changes in multiple organs and organ systems, there are many age-related differences. These include body composition, changes in liver mass, changes in renal function, etc., all of which have implications in drug absorption and metabolism.

Beyond age-dependent differences, it is also essential for sponsors to have knowledge about pathophysiology, tumor location and type, potential risk factors, toxicity differences and even preferred formulation methods that can impact the clinical trial design and help develop appropriate chemotherapeutic treatments for children.

From the operational perspective, sponsors will need to be more proactive in their approach and incorporate earlier preclinical testing, such as next-generation multi-omic data, to better determine appropriate pediatric clinical studies and reduce unnecessary testing of early-phase molecules. Consortia, such as the NCI PPTC and ITCC-P4, and key opinion leaders can help guide evolving models in the treatment landscape. Research tools can also be adapted for children and adolescents to improve toxicity reporting in clinical trials, validate quality of life (QoL) measurements and incorporate overall survival (OS) and event-free survival (EFS) metrics to quantify improvements and help shape new therapeutic strategies in oncology.

Looking Ahead to Improve Cancer Therapies for Children

Even though remarkable progress has been made in the scientific community's understanding of the genomic landscapes of pediatric cancers, pediatric subpopulations are highly variable and multiple factors play into the design of a trial.

In today's era of mechanism of action and targeted treatments, sponsors must evaluate multiple considerations of how to best approach their pediatric trial designs. With the RACE for Children Act in the U.S. and similar incentive and requirement programs in the EU, it's evident that there can – and will be – a greater impact to global development by encouraging the development of more oncology treatment options that may improve the health and quality of life for pediatric patients around the world.

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Disclosures:

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