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REVIEW ARTICLE

Navigating the Regulatory Landscape to Develop Pediatric Oncology Drugs: Expert Opinion Recommendations

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Abstract

Regulatory changes have been enacted in the United States (US) and European Union (EU) to encourage the development of new treatments for pediatric cancer. Here, we review some of the factors that have hampered the development of pediatric cancer treatments and provide a comparison of the US and EU regulations implemented to address this clinical need. We then provide some recommendations for each stage of the oncology drug development pathway to help researchers maximize their chance of successful drug development while complying with regulations. A key recommendation is the engagement of key stakeholders such as regulatory authorities, pediatric oncologists, academic researchers, patient advocacy groups, and a Pediatric Expert Group early in the drug development process. During drug target selection, sponsors are encouraged to consult the Food and Drug Administration (FDA), European Medicines Agency (EMA), and the FDA target list, in addition to relevant US and European consortia that have been established to characterize and prioritize oncology drug targets. Sponsors also need to carefully consider the resourcing requirements for preclinical testing, which include ensuring appropriate access to the most relevant databases, clinical samples, and preclinical models (cell lines and animal models). During clinical development, sponsors can account for the pharmacodynamic (PD)/pharmacokinetic (PK) considerations specific to a pediatric population by developing pediatric formulations, selecting suitable PD endpoints, and employing sparse PK sampling or modeling/simulation of drug exposures where appropriate. Additional clinical considerations include the specific design of the clinical trial, the potential inclusion of children in adult trials, and the value of cooperative group trials.

Plain Language Summary

In the last few decades, great progress has been made in developing new treatments for adult cancers. However, development of new treatments for childhood cancers has been much slower. To encourage drug companies (sponsors) to develop effective treatments for childhood cancer, authorities in the United States (US) and Europe have made new rules for drug development. Under these new rules, sponsors developing drugs for specific cancers in adults have to consider whether the target of that drug also causes cancers in children. If this is the case, sponsors have to carry out clinical studies of their drug in children who have cancer that is caused by the same drug target. In this article, we describe some reasons for why drug development for childhood cancers has been slow and the rules created to address this problem in the US and Europe. We share some recommendations to help sponsors maximize their chances of developing an effective drug in children while satisfying the new rules. Specifically, sponsors need to be aware of the differences between studying drugs in adults versus children and how these influence the way the drug is tested. We make several recommendations for each stage of the development process, beginning with what is needed even before human studies begin. Finally, we highlight some issues that sponsors need

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to think about during drug development, from the preclinical stage (testing drugs in cells and animals) through to clinical testing in adults and pediatric patients with cancer.

Key Points

Drug development for pediatric cancers has been slower than for adult cancers, and regulatory authorities in the United States and the European Union have introduced legislation to accelerate pediatric drug development.

To comply with the new regulations, sponsors need to consider the need for studies in a pediatric population, for each drug being developed.

Compared with adult studies, the specific needs of a pediatric population may require changes in the assessment of preclinical rationale and translational relevance, formulation development, pharmacokinetics/pharmacodynamics, clinical endpoints, and clinical trial design.

1 Introduction

1.1 Background

Cancer is one of the leading causes of death by disease in children in high-income countries [1]; in Europe and North America, 20% of children with cancer die from their disease [2]. For children 0 to 14 years of age in the United States (US), the National Cancer Institute (NCI) estimated that in 2018, 10,590 would be diagnosed with cancer, resulting in 1180 deaths from the disease [3]. In the last few decades, considerable progress has been made in the treatment of pediatric cancers, with the 5-year survival rate for children with cancer overall in high-income countries currently at ~80% [4], with some types of cancer faring significantly better. Despite this progress, there are still major unmet needs in this patient population. The 5-year survival rates [4] for children with cancer in middle- and low-income countries are ~ 55% and ~ 40%, respectively, and survival prospects for several pediatric cancers are still very poor. Children with diffuse intrinsic pontine glioma have a 2-year survival rate of < 20%, with essentially no long-term survivors [5]. Children with cancer who have recurrent, relapsed, or refractory disease also have very poor survival. Among pediatric patients who are long-term survivors, many have long-term sequelae as a result of the aggressive surgery, chemotherapy, and radiotherapy regimens received [6, 7].

Pediatric cancers often differ from adult cancers in terms of the organs affected and the tissues and biology of origin. Most adult malignancies, such as lung, breast, and colorectal cancers, are carcinomas that develop from epithelial tissue. In contrast, the vast majority of pediatric cancers, including leukemias, lymphomas, and sarcomas, develop from the mesoderm. To better understand the genetic drivers of cancer, several studies have examined the differences and similarities in the molecular alterations encountered in different adult cancers (pan-cancer analyses). Researchers recently performed similar analyses for pediatric cancers [8, 9]. Pediatric cancers are thought to have 'quieter' genomes compared with adult cancers, and had mutation frequencies 14 times lower than adult cancers [8]. Despite having fewer genetic aberrations than adult cancers, many pediatric cancers have underlying genetic drivers that are already well characterized in adult cancers. Ma et al. reported that 45% of the driver genes in pediatric cancer matched genes identified in the adult pan-cancer studies [9]. For drugs targeting genes that drive both pediatric and adult cancers, the findings from clinical trials in adults can be used to guide clinical trials of the same drug in a pediatric population. Grobner et al. reported that ~50% of pediatric tumors may contain an alteration in a gene for which a directly or indirectly targeted treatment is available or under development [8].

However, a large proportion of the genetic drivers in pediatric cancer do not overlap with those of adult cancers [8, 9]. In most cases, treatments targeting molecular alterations specific to pediatric cancers are yet to be developed, and the pediatric cancer field has had to rely on targeted agents for adult indications. The development and advancement of high-throughput sequencing technology has spurred the rise of the personalized medicine paradigm in the treatment of adult cancer. A similar paradigm shift is occurring in pediatric oncology [10]. Recent advances in the understanding of biomarkers and tumor biology, coupled with recognition of the 'quieter' genomes of pediatric cancers, highlight the value of adopting a drug development strategy with a mechanisms-of-action (MoA)-driven approach [2]. The success of this approach is exemplified by tumor-agnostic therapies such as nivolumab and larotrectinib [11]. Nivolumab targets programmed cell death protein-1 and is approved for the treatment of adult and pediatric (aged ≥ 12 years) patients with mismatch repair deficient/microsatellite instability-high metastatic colorectal cancer that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [12]. Larotrectinib inhibits the TRK receptor family and is approved for the treatment of adult and pediatric patients

with solid tumors with a *NTRK* gene fusion without a known acquired resistance mutation [13].

Although significant progress has been made in the development of therapies to treat adult cancers over the last 20 years, progress has been much slower for pediatric cancers [14]. During a 5-year period in the European Union (EU), 26 oncology drugs approved to treat adults were found to have MoA potentially relevant to pediatric cancers. However, only four of these drugs were approved for use in children [15]. The median time from when an oncology drug is first tested in adults to when it is tested in children is 6.5 years. In some cases, the delays can be substantially longer, up to ~ 28 years [16].

1.2 Delayed Development of Treatments for Pediatric Cancer

It has long been recognized that pediatric drug development poses additional challenges on top of those encountered during adult drug development. These challenges include the relatively low incidence of some diseases in children, differences in disease manifestation between adults and children, and the lack of age-appropriate, clinically validated endpoints [17], all of which also apply to the development of oncology drugs for a pediatric population. Compared with adults, cancers in children are relatively rare. More than 1.7 million new cases of cancer were projected in the US in 2019, and fewer than 1% of these were expected to be in children 0–14 years of age [18]. Small patient numbers have an impact not only on clinical studies, but also on the preclinical and translational research conducted to build a rationale for clinical studies. Fewer patients translates to fewer tumor samples available for study, hindering molecular characterization of the disease and the availability of appropriate preclinical models to assess potential therapeutics; however, this can often be overcome by multi-institutional cooperation. This type of cooperation is exemplified by the collaborative research groups that have been established for pediatric oncology drug development, including the Children's Oncology Group (US-centric), the Innovative Therapy for Children with Cancer Consortium (ITCC; Europe), the Children's Cancer and Leukaemia Group (UK), and the Nordic Society of Paediatric Haematology and Oncology (Europe). For clinical studies, smaller pediatric patient numbers (compared with adult patients) make it even more important to recruit sufficient numbers of patients from multiple institutions and to conduct multi-national clinical trials to explore therapeutic interventions in a timely manner. Smaller patient numbers also mean that fewer trials for any given cancer type can be conducted within a given time; some clinical trials remain open for years in order to recruit sufficient numbers of patients. Some trials are unable to produce data that are statistically meaningful as they lack sufficient patients. The small number of pediatric patients relative to adult patients also means that there is a lack of commercial incentive to develop pediatric treatments.

The reluctance to pursue pediatric drug development may also stem from concerns about the potential for pediatric-specific drug toxicity. There may also be concerns that safety signals identified in the pediatric population may jeopardize the adult drug development program. However, there is little evidence of unique, acute drug toxicities observed in children that are not already known in adults receiving the same drug. In some cases, pediatric patients are often able to tolerate therapies better than adults [19].

1.3 Regulatory Initiatives

1.3.1 US Regulations

The *Best Pharmaceuticals for Children Act* (BPCA) [20] was passed in the US in 2002; under this act, the US Food and Drug Administration (FDA) can issue a 'Written Request' to sponsors to conduct pediatric studies, although fulfillment of such requests are voluntary. Sponsors are also able to submit a proposal to the FDA to obtain a Written Request. In return for fulfilling a request within the agreed timeframe, sponsors can obtain a 6-month period of marketing exclusivity (Table 1).

In 2003, the US Congress passed the *Pediatric Research Equity Act* (PREA) [21]. Under PREA, sponsors seeking approval from the FDA for a new chemical entity, new indication, dosage form, dosing regimen, or route of administration are required to include a pediatric assessment in the initial New Drug Application (NDA), Biologics License Application (BLA), or supplements to NDA/BLA submissions, unless the applicant has received a waiver or deferral. Under PREA, the requirement for pediatric assessment pertained only to the indications included in the pending adult application, and the need for pediatric studies was waived if that condition did not occur in children (e.g., breast, lung, or prostate cancer), even if the molecular target was relevant to a pediatric disease. In addition, PREA originally did not require pediatric studies for drugs developed for orphan indications. These indications included molecularly targeted adult cancer types (i.e., leukemias, lymphomas) that also occur in children, as well as targets relevant to pediatric-specific cancers for which the adult indication was orphan (e.g., anaplastic lymphoma kinase [ALK]+ neuroblastoma and ALK+ non–small-cell lung cancer).

The limitations of PREA coupled with the advent of personalized medicine led the US Congress to pass the *Research to Accelerate Cures and Equity (RACE) for Children Act* in 2017, which was fully in effect as of August 2020, to further encourage the development of therapies for pediatric cancers [22]. The *RACE for Children Act* amends

Table 1 Comparison of regulatory requirements in the US vs the EU [28]

	US BPCA	US PREA (following the *RACE for Children Act*)	EMA EC 1901/2006
Voluntary/mandatory	Voluntary	Mandatory	Mandatory
Incentive	6-month patent extension	None	6-month patent extension*
Document	Written request from FDA	iPSP	PIP
Products with orphan designation	Included	Included if *RACE for Children Act* stipulation met	Included
Timing of submission of plan/waiver request	When data are available—must be submitted before loss of exclusivity to receive the incentive	End of phase 2 in adults and before phase 3 (required before submission of NDA/BLA)	Ideally at the end of phase 1 in adults
Decision-making body	FDA PeRC	FDA PeRC	EMA PDCO

BLA Biologics License Application, *BPCA Best Pharmaceuticals for Children Act*, *EMA* European Medicines Agency, *EU* European Union, *FDA* Food and Drug Administration, *iPSP* initial pediatric study plan, *NDA* New Drug Application, *PDCO* Paediatric Committee, *PeRC* Pediatric Review Committee, *PIP* pediatric investigation plan, *PREA Pediatric Research Equity Act*, *RACE* Research to Accelerate Cures and Equity, *US* United States

*Orphan-designated products may be granted a 2-year extension of exclusivity

the PREA and contains two key components (only applicable to 'new molecular entities'): (1) applications for a study drug that "is intended for the treatment of an adult cancer and is directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer" have to include a pediatric study investigation [23] (unless waived or deferred); (2) for drugs designated with orphan status, the PREA exemption no longer applies if the drug's target meets the aforementioned definition of a molecular target [22]. A recent analysis of 78 cancer drugs suggested that enactment of the *RACE for Children Act* may mean that ~ 80% of cancer drugs may be subject to pediatric study requirements [24].

The *Creating Hope Act* is another piece of US legislation that may have an impact on pediatric drug development. This act was established in 2012 to provide sponsors with an incentive to develop treatments for rare pediatric diseases. [25] Following development and approval of a drug targeting a rare pediatric disease, a sponsor may be awarded a priority review voucher (PRV). The PRV allows a sponsor to shorten the FDA review period of a future drug from the standard 10 months to 6 months. In December 2020, the Pediatric Disease PRV Program was extended [26].

1.3.2 European Regulations

In Europe, the European *Paediatric Regulation* (EC 1901/2006) was enacted to increase the development of treatments for children and adolescents aged 0–17 years [27]. Adult drug development plans in Europe require a pediatric investigation plan (PIP) be submitted "not later than upon completion of the human PK [pharmacokinetic] studies" [28]. Sponsors that submit pediatric data fulfilling a PIP in advance of a drug's loss of exclusivity date will obtain a 6-month extension on a product's supplementary protection certificate. The Paediatric Committee of the European Medicines Agency (EMA) has compiled a class waiver list based on the following criteria [29]: (1) treatments that are likely to be ineffective or unsafe in a pediatric population, (2) do not represent a significant therapeutic benefit over existing treatments for pediatric patients, or (3) target conditions that only occur in adults. For companies developing drugs that fit these criteria, the requirement to submit a PIP is waived as per article 11b of the European *Paediatric Regulation* [27]. Drugs developed for a condition on the waiver list are automatically granted a waiver, without the need for the sponsor to provide any justification. There have been concerns that class waivers may actually hinder the development of pediatric drugs. For instance, drugs that have been granted a waiver because they were developed against a disease occurring only in adults may still be worth investigating in a pediatric population if they target molecular drivers important for pediatric cancers [30]. Some of these concerns have been addressed by recent revisions to this list in 2018, which significantly reduced the number of conditions for which waivers are granted [29]. For drugs targeting conditions no longer on the waiver list, sponsors will have to file a specific application for a waiver.

In 2020, the EU initiated an impact assessment of the regulation for medicines for rare diseases and the regulation for medicines for children in order to address the shortcomings in both regulations. A number of different options are currently being considered to replace/revise the incentive scheme currently set out in the regulation for medicines for children [31].

Sponsors should consider both US and EU regulatory requirements during the early stages of drug development to ensure compliance with both agencies and minimize

duplication of drug development efforts, especially given the small pool of eligible pediatric patients. In September 2020, the FDA and EMA produced a joint publication strongly encouraging sponsors to coordinate planning and submission of initial pediatric study plans (iPSPs)/PIPs to the appropriate regulatory agencies [32]. Though similar, there are notable differences between US and EU pediatric regulations (Table 1) [28, 33]. In the US, the requirement to conduct pediatric studies is governed by PREA, whereas the incentive to perform pediatric studies is governed by BPCA. In the EU, both the incentive and the requirement for studies are contained within one piece of legislation [28]. In terms of timing, to comply with PREA, companies in the US are encouraged to submit an iPSP before the initiation of registrational (or pivotal) studies, but submission can occur up to 210 calendar days before submission of a marketing application [28]. In the EU, submission of the PIP should ideally take place after phase 1 of the adult study [28]. In the US, failure to submit a pediatric study plan (PSP) with the application where required may be grounds for the FDA to refuse to file an application [34]. Non-compliance with the EU *Paediatric Regulation* results in the application being rejected for use in either children or adults [27].

The regulatory changes described above are likely to have a significant impact on oncology drug development programs. The purpose of this article is to help sponsors, clinicians, and academic researchers navigate these regulatory requirements by providing a number of key recommendations to help optimize the drug development pathway for pediatric oncology. We outline key considerations for preclinical/translational, pharmacokinetic (PK)/pharmacodynamic (PD), and clinical development (Fig. 1). We hope that adoption of these recommendations will help sponsors accelerate the development of new oncology treatments for pediatric patients while complying with the regulatory requirements in each region.

2 Key Recommendations: Early Engagement of Key Stakeholders and Patient Representatives, and the Formation of a Pediatric Expert Group

Before commencing a clinical development program, sponsors should consider engaging with key stakeholders to maximize the chances of program success. Sponsors should initiate discussions with the appropriate regulatory agencies (e.g., EMA Paediatric Committee, FDA Pediatric Review Committee, FDA Oncology Subcommittee of the Pediatric Review Committee, and Oncology Center of Excellence) during the early stages of drug development. Where possible, sponsors should conduct joint meetings with the FDA and EMA to align international agency discussions and maximize the efficiency of the pediatric development plan. It is worth noting that the EMA and FDA have themselves initiated regular meetings ('clusters') that also include other regulatory agencies, to discuss specific topics of mutual interest [35]. Given the importance of patient-reported outcomes (PROs) in oncology trials, clinical development programs also need to engage personnel with expertise in developing and measuring PROs specifically in a pediatric population [36]. Early engagement of key opinion leaders

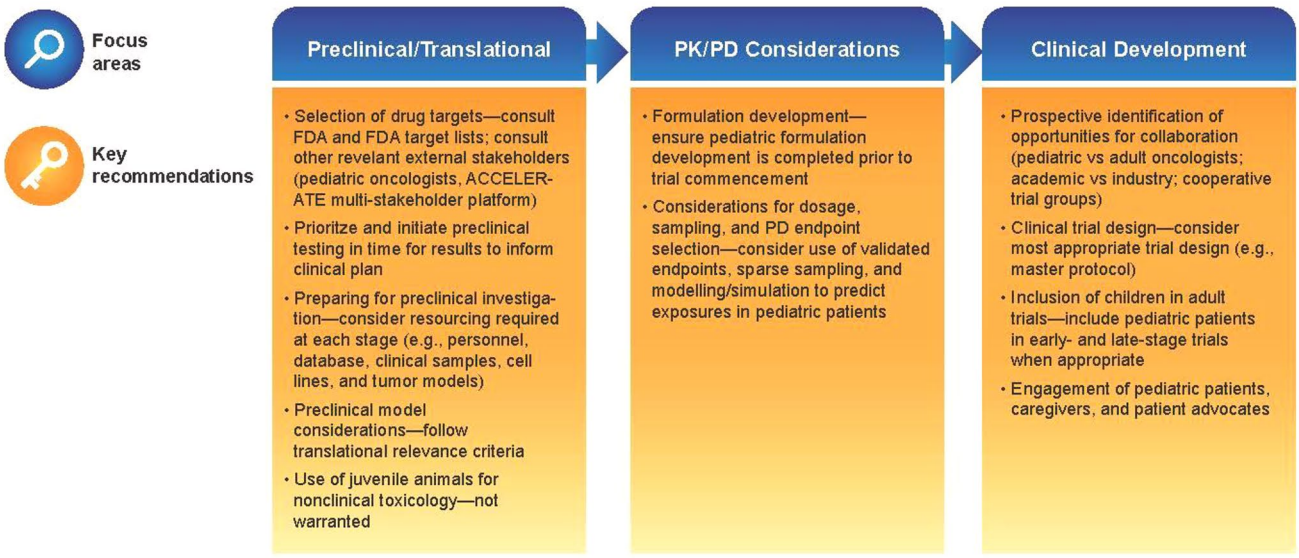

Fig. 1 Key recommendations for pediatric oncology investigation. *FDA* Food and Drug Administration, *PD* pharmacodynamics, *PK* pharmacokinetics

and academic collaborators may be helpful for refining the drug development strategy.

There is growing recognition of the value provided by greater engagement of patients and their caregivers in the drug development process. Patient involvement in clinical research may improve the outcomes achieved, by focusing studies on what is most relevant from a patient perspective. Further, patient engagement can also enhance clinical trial design and result in higher rates of enrollment and retention [37, 38]. Efforts are already underway to involve pediatric patients, caregivers, and patient advocates in various aspects of clinical research, including the planning and design of clinical studies [39]. Pediatric patient advocacy groups can play an important role in facilitating interactions between patients and sponsors [40]. The International Children's Advisory Network, a worldwide consortium of child and family advisory groups, allows researchers or sponsors to engage patient advisers and families to obtain their feedback on different aspects of clinical trials, including trial designs and logistics as well as consent and assent forms [41].

Several pharmaceutical companies have also established a Pediatric Expert Group (PEG) to better support the process of pediatric drug development [42]. As described by Severin et al., the structure as well as the roles and responsibilities of a PEG vary depending on the company [42]. Some PEGs have limited involvement with the pediatric drug development program, serving only as consultants, whereas other PEGs have ownership of and responsibility for the program [42]. Common to all PEG structures is an emphasis on medical functions, with expert pediatricians usually appointed to the group. Representatives with expertise in preclinical/translational, regulations, clinical operations, and clinical pharmacology/pharmacometrics are also commonly appointed to PEGs [42]. Irrespective of how they are implemented, PEGs constitute a valuable resource for sponsors pursuing pediatric drug development.

3 Key Recommendations: Preclinical/Translational

3.1 Selection of Drug Targets

Given the large number of potential molecular targets and the limited pool of pediatric oncology patients for clinical trials, it is critical to ensure efficient enrollment of patients into the most appropriate trials. This begins with the selection of drug targets most likely to be drivers of pediatric cancers. As part of the *RACE for Children Act*, the FDA has developed a Pediatric Molecular Target List [43], which includes (1) "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" and (2) "those targets for which there is evidence that they are not associated with the growth or progression of pediatric tumors for which requirement for early pediatric evaluation of drugs and biologics which are directed at these targets would be waived."

The pediatric platform ACCELERATE, created in 2015 in Europe, recommends the creation of an aggregated, publicly available database of tumor targets [30]. This database should enable easier evaluation of molecular targets (based on MoA) that may warrant further preclinical or clinical investigation in a pediatric population and allow prioritization of the most relevant drug targets [2, 30]. ACCELERATE also organizes Paediatric Strategy Forums to bring together stakeholders (including patient advocates, academics, pharmaceutical representatives, and regulatory authorities) to help prioritize drugs, targets, and disease areas [44–46]. Several consortia have also been formed to facilitate preclinical testing of drugs and targets for pediatric cancer indications. The Pediatric Preclinical Testing Program (PPTP), sponsored by the US NCI, has been operating productively for several years, yielding dozens of publications on drug screens in various pediatric cancer models [47]. A European consortium formed the Innovative Therapy for Children with Cancer Paediatric Preclinical Proof-of-Concept Platform (ITCC-P4), a joint academic–pharmaceutical industry platform to characterize and prioritize targets in high-risk pediatric solid tumors [30, 48] and facilitate tumor model development and drug screening. A pediatric preclinical public–private partnership is also being considered in the US [49]. These platforms and initiatives may also foster a more collaborative approach among pharmaceutical companies.

3.2 Prioritization and Timing of Preclinical Testing

A collaborative approach is ideal for drug prioritization, as a highly coordinated effort could deliver preclinical results comparing the activity of different drugs in the same models. All potential drug candidates directed to the same molecular target could be compared for relative efficacy in appropriate target-driven models. In cases where more than one MoA is predicted to have benefit in the same specific indication, a similar preclinical comparison could be conducted with drugs addressing different MoAs tested in the same models. The most promising of the new drug candidates could then be benchmarked against the current standard of care (if one exists for that indication) and only taken forward if they demonstrate meaningful advantages. The best performing preclinical compound would then warrant clinical testing over the other candidate drugs and mechanisms, thereby best serving the limited pool of pediatric patients. This level of collaboration and coordination is a hopeful future extension of efforts by consortia like ACCELERATE and ITCC-P4,

as well as the pediatric oncology research and development and regulatory communities. Realization of this future state requires an unprecedented level of cooperation between pharma companies and would ideally be bolstered by additional incentives from regulatory authorities; incentives could include the granting of waivers (if requested) for new drugs tested in this collaborative manner when the new drug tested is not a 'winner.'

Pediatric development plans should be submitted to regulatory authorities early in the adult drug development pathway. Ideally, the completed pediatric study reports should be submitted at the time of a marketing application. If this is not feasible, a deferral to submit the reports at a later date should have been incorporated in the PSP/PIP. Before initiating pediatric clinical studies, the pediatric plan should be well-supported by completed preclinical studies, demonstrating the potential for the new drug in the pediatric indication of interest. This may require initiation of pediatric preclinical work at an early stage (ideally before phase 1 adult testing), in order to complete the pediatric preclinical evaluation in time for the required PSP/PIP submissions. For pharmacology studies, access to appropriate preclinical models may require collaboration or licensing, adding to the timeline. What constitutes a sufficient preclinical data package to support pediatric clinical testing is a challenging question that has been addressed in position papers [50, 51] and briefly in a recent guidance document co-published by the FDA and the EMA [52]. This will also be dependent on the MoA of the drug and the availability of relevant pediatric models appropriate for testing that MoA. Sponsors may also leverage their experience with what constitutes sufficient preclinical data to support clinical development in adult cancer indications and apply that standard to pediatric indications.

3.3 Preparing for Preclinical Investigation: Adequate Resourcing

To mitigate some of the risks involved with drug development, we recommend that sponsors concentrate their initial efforts on focused preclinical development. These preclinical analyses define the potential pediatric indication(s) and form the foundation for a thoughtful pediatric drug development strategy, including pediatric dosage form requirements. Although preclinical development entails a relatively modest investment, it can provide valuable guidance for subsequent stages of drug development. Preclinical assessment allows sponsors to benchmark the activity of new drugs to standard-of-care agents and to differentiate between molecules that may bring benefit to the small population of pediatric patients available for clinical trials versus molecules that are unlikely to be active in a clinical setting.

For sponsors to marshal sufficient resources for preclinical investigation, it is vital to know the scale and types of preclinical studies required. For drug targets not listed on the FDA's relevant target list or the non-relevant target list (i.e., relevance not yet determined), the current FDA guidance provides a good outline of specific studies needed to establish relevance. In addition, Schubert et al. recently published a more comprehensive framework of key experimental evidence for assessing target relevance and priority [48]. However, as the FDA is tasked with establishing relevance, it is unclear to what extent the sponsor is required to invest in such research. In order to reduce bias, it may be more appropriate to shift the responsibility for carrying out basic research to determine the relevance of a drug target to pediatric cancers away from sponsors. To better assist sponsors with appropriate resourcing, the current FDA guidance around the requirements for preclinical data could be improved by the inclusion of more details on the specific studies needed, if any, for targets listed on the relevant target list, in order to support (or refute) the rationale for clinical evaluation in pediatric patients. For example, a single sentence in a recently co-published guidance document from FDA and EMA [52] helps guide sponsors on preclinical studies for induced pluripotent stem cells and PIPS: "Provide results of pre-clinical assessment of activity of a product in relevant paediatric-specific models both in vitro and in vivo as well as potential pre-clinical combinations." If preclinical/clinical data demonstrate that a program is not viable and a waiver request is being considered, the burden of proof rests with the sponsor. Here again, guidance or examples from the FDA on what constitutes a sufficient data package to support a waiver request would be helpful for sponsors when allocating resources.

Other key considerations for preclinical development are collaborations with academic partners studying relevant diseases and MoAs, and timely procurement of resources, including personnel, genomics database access, computational biology expertise, clinical samples, and appropriate cell lines and tumor models.

3.4 Preclinical Model Considerations

The choice of cell lines, tumor models, and preclinical doses needs to be carefully considered when developing therapies for a pediatric population [50]. The cell lines, xenografts, and genetically engineered mouse models utilized should be representative of or derived from pediatric cancers and should have direct translational relevance to the pediatric population. Langenau et al. proposed ten criteria (Table 2) that need to be met in order to establish the translational relevance of a particular preclinical model for pediatric cancer [51]. These criteria include the use of clinically relevant doses, combinations, and schedules, as well as tumor validation and efficacy measurements that

Table 2 Criteria to enable evaluation of the translational relevance of preclinical models of pediatric cancer (developed by St. Jude Children's Research Hospital) [51]

Criteria	Description
Randomization	Before the preclinical study begins, the randomization schedule should be designed by biostatisticians and the interim analysis and censure rules specified
Double-blind study design	Individuals administering treatment and monitoring responses should have no knowledge of the treatment groups
Pharmacokinetics	The murine equivalent dose should be determined based on the recommended pediatric phase 2 dose (RPP2D). In many cases, the RPP2D is not known, so the adult recommended phase 2 dose is used instead
Pharmacodynamics	Pharmacodynamic analysis is required to confirm that the drug enters tumor cells and affects the pathway of interest
Clinically relevant drug dose	The drug dose used in the preclinical model should correspond to the plasma exposure in pediatric patients (if known)
Clinically relevant drug combination	In addition to single-agent studies, drug combinations should be considered for preclinical studies if clinically relevant
Clinically relevant drug schedule	The duration of each course of therapy in the preclinical study should be the same as that used in clinical trials
Monitoring toxicity relevant to pediatric patients	The hematological and/or organ toxicity expected for a given treatment should be carefully monitored and any relationship between drug exposure and toxicity should be characterized
Tumor validation	Preclinical tumor model should be carefully characterized and, where possible, should match patient tumors in terms of histology, genomic features, and tumor location
Efficacy measurements relevant to patient outcome	The definitions of progressive disease, stable disease, partial response, and complete response should be specified before the preclinical study begins. As a guide, for a double-blind, placebo-controlled, randomized efficacy study, typically 10–20 mice per group are needed to adequately power the study

are relevant to a pediatric population [51]. Of particular importance in preclinical models is how a response is measured and what magnitude of response constitutes a positive result.

Initiatives such as the PPTP (solid and hematological cancers) and ITCC-P4 (solid tumors) enable sponsors to test compounds in models for a variety of pediatric cancers, including leukemias, sarcomas, and neuroblastomas, as well as central nervous system, renal, and hepatic cancers [53]. Given the dearth of effective treatments for metastatic, recurrent, or relapsed disease, the use of appropriate preclinical models for these disease states (when available) should also be considered. The models used should also be representative of the different molecular subsets within a given disease. For example, there are now four major molecular subtypes of medulloblastoma that are recognized, each of which may respond differently to a given targeted agent. Preclinical models can help tailor human use to be as safe and as efficient as can be predicted. It is important, however, to acknowledge some of the limitations of current preclinical models. Models developed in immunocompromised mice cannot be used to assess the activity of oncology drugs that target the immune system. Moreover, it has yet to be firmly established that the activity of a drug in a pediatric patient-derived xenograft model is predictive of drug activity in pediatric patients. Further research and development of new pediatric preclinical models are required.

Careful consideration of the range of exposures required to observe a response is also important when deciding whether to proceed with development of a drug for use in children. If a response can only be observed at exposures that are not clinically achievable in pediatric patients, further development of the compound should not proceed. If available, PK data from adults can be used to guide dose levels used for in vitro and in vivo testing [50].

3.5 Use of Juvenile Animals for Nonclinical Toxicology

The International Conference on Harmonisation (ICH) S9 guidance for advanced cancer indications provides nonclinical recommendations for studies needed before initiating clinical trials and during drug development, including pediatric drug development [54]. Under ICH S9, studies in juvenile animals are not usually warranted to support inclusion of pediatric populations for treatment of advanced cancers. The use of juvenile animal models was previously proposed by the EMA and the FDA for cases where safety data from adults and animal toxicology studies were lacking but there was sufficient justification (based on MoA, target expression, or impact on growth and development) for evaluating

the suitability of a compound for a pediatric trial [55, 56]. After this guidance was issued, the utility of juvenile animal studies to support pediatric drug development was further evaluated [57, 58].

In general, retrospective analyses indicated that differences in sensitivity between adult and juvenile animals were not considered sufficiently significant to warrant additional juvenile studies. Instead, these differences can be addressed through clinical safety monitoring and fractionation of doses based on body surface area [59]. Analyses across approved small molecule and biologic drugs support a strong correlation between the maximum tolerated doses for adult and pediatric patients [19, 60]. Additional literature concluded that juvenile animal studies are not needed in order to safely conduct phase 1 clinical trials in pediatric patients, either for selecting a safe starting dose or informing on potential toxicities that may be unique to a pediatric population [61]. There is some debate on this last point, and it has been suggested that there may be additional sensitivity to some drugs in developing animals, sufficient to warrant a case-by-case approach to evaluate the need for a juvenile toxicity study [62].

The type of toxicity identified in a preclinical model may have different ramifications for a pediatric population compared with an adult population. Identification of preclinical toxicities such as impairment of growth, development, or reproductive potential is of particular importance to a pediatric population. However, this assessment should be balanced with the fact that current effective but aggressive therapeutic regimens for various pediatric oncology indications have significant long-term health effects that occur at high frequencies in survivors [6, 7].

4 Key Recommendations: PK/PD Considerations

4.1 Formulation Development and Administration

A key consideration for pediatric trials is the method of drug administration. Although oral formulations are commonly used in adult trials [15], young children may have difficulty swallowing tablets or capsules [63]. Mini-tablets or dispersible/dissolvable powder for oral suspension formulations are a recommended alternative to regular tablets or capsules and may result in higher compliance in a pediatric population. In some cases, however, the strength of the formulation may limit the degree to which the dosage can be adjusted. Liquid formulations are commonly used for pediatric populations, and the inclusion of children into an existing adult trial that uses tablets/capsules may necessitate development and testing of a liquid formulation, which should be done well in advance of pediatric enrollment [63]. Developing liquid formulations for a pediatric population requires careful evaluation of the excipients used as they may be harmful to children despite being regarded as safe in adults [64, 65]. Excipients may also affect bioavailability, necessitating an increase in dosage [66]. In addition, a portion of pediatric patients with cancer may require enteral feedings by tube, so adsorption to plastics is an important factor to consider if the agent will be administered by this route.

Another strategy for drug administration in pediatric populations is the use of extemporaneous formulations. This usually involves the conversion of existing tablets or capsules into a liquid dosage form that is more easily administered to children. However, given the risks associated with extemporaneous compounding, the focus should be on the development of formulations appropriate for a pediatric population.

4.2 Dosing

When deciding on the optimal starting dose, an important consideration is the type of therapeutic under study; large-molecule drugs such as monoclonal antibodies may require different approaches to cytotoxics or targeted oral therapies [66]. For diseases where the exposure–response relationship in adults is sufficiently similar to that in children, modeling and simulation approaches (e.g., allometric scaling and physiologically based PK modeling and simulation) may be useful for predicting exposures in pediatric patients. One approach is to begin dosing at the recommended dose level for adults, adjusting appropriately for body surface area, which seeks to minimize dosing and therefore patient exposure at sub-therapeutic levels.

4.3 PK Sampling Considerations

The heterogeneity of the pediatric patient population (which may span a range of body weights and developmental stages) compared with adult patients may require modification of sampling procedures, dosing algorithms, and endpoint selection [66]. Depending on their age, children can differ significantly from adults in terms of their absorption, distribution, metabolism, and excretion of various chemical compounds [17]. Further, there are important differences in PK within the pediatric population (infants vs children vs adolescents/young adults) [67]. Owing to the limited number of samples and blood volumes that can be safely collected in children, the intensive blood sampling schemes applied to adults are often not appropriate in the pediatric context [68]. As an alternative, where the metabolic pathways are well defined in adult

patients, sparse PK sampling approaches allow for fewer samples to be taken per patient [66].

4.4 PD Endpoint Selection

The use of biomarkers to assess disease progression and treatment response is a critical component of clinical trials in adults. However, despite the historical extrapolation of adult biomarkers to children, using biomarkers validated in adults is not always appropriate for pediatric patients [69]. To address these issues, it is critical that PD endpoints are carefully validated before use, to ensure that they are both meaningful and reproducible [69]. The heterogeneity of the pediatric population and the difficulty of obtaining appropriate age-matched control samples from healthy children are just some of the factors hampering the validation of pediatric biomarkers [17]. Another important factor is the difficulty in obtaining serial biopsies of pediatric solid and brain tumors in order to assess biomarkers in patients with relapsed disease or to examine PD measurements of target engagement. It is hoped that less invasive techniques such as blood biopsy (e.g., circulating tumor cells and circulating tumor DNA) may enable accurate PD assessment in the future.

5 Key Recommendations: Clinical Development

5.1 Prospective Identification of Opportunities for Collaboration

Before beginning clinical development of a compound, guidance should be sought from pediatric oncologists, especially those with clinical research expertise. Close collaboration between adult and pediatric oncologists is also strongly encouraged to ensure maximal alignment between adult and pediatric programs. The presence of an existing PEG (above) can help ensure these collaborations are established in an effective and timely manner.

As outlined above, fewer pediatric patients are available for clinical trials, compared with adult oncology populations. However, compared with the small proportion (~8%) [70] of adult cancer patients enrolled in clinical trials, trial enrollment is more common among pediatric cancer patients, with enrollment rates between 19.9% and 27.5% reported in the US [71], Canada [72], and New Zealand [73]. However, disparities have been observed in the proportion of patients enrolled across different pediatric age groups; notably, the proportion of adolescents participating in clinical trials is often smaller than for younger children [71].

To recruit sufficient numbers of patients, pediatric oncology studies often need to be spread across multiple sites and sometimes countries, leading to increased logistical challenges and higher infrastructure costs, compared with trials utilizing fewer sites/countries. Therefore, developing therapeutics for pediatric oncology may require more infrastructure and longer lead times than for adult cancer [74]. Cooperative group trials were established to meet some of the challenges associated with conducting large multicenter studies. The Children's Oncology Group was formed in 2000 from five legacy groups in North America, Australia, New Zealand, Japan, and Switzerland, and is currently the world's largest research organization focused on pediatric cancer research [75]. European consortia such as the ITCC [76] and European Society for Paediatric Oncology (SIOPE) [77] bring together a number of clinical trial groups, many of them spanning several different European countries. In addition to cooperation between academic research centers, close collaboration between industry and academic investigators is also important for the success of pediatric oncology trials.

5.2 Clinical Trial Design

Modifications to the traditional design of clinical trials may increase the speed of pediatric drug development. Bayesian approaches enable utilization of adult trial data to compensate for the smaller sample sizes in pediatric oncology [78]. Based on a review of the statistical trial designs used in phase 1 pediatric oncology trials (published between 2009 and 2014), Doussau et al. suggested that model-based designs (e.g., continual reassessment method) may be better at identifying the target dose, compared with the more frequently used algorithm-based designs (e.g., 3 + 3 and Rolling 6) [79]. The use of pediatric master protocols may also be advantageous, as they allow for multiple treatment cohorts, whereby patients are assigned to receive a specific targeted therapy matched to their unique tumor profiles (based on molecular screening) with the drug target/MoA [80, 81]; this approach is being used in the Pediatric MATCH trial for solid tumors [82] and the LLS PedAL initiative for leukemia [83].

Earlier assessment of combination treatments (as opposed to single-agent treatments), shortening the dose-determination phase of trials, extrapolation of PK and PD data from adult trials, and harmonization of response criteria may also accelerate pediatric drug development [84]. The concept of 'treatment beyond disease progression' for patients who are deriving clinical benefit is increasingly used in adult cancer trials [85–87] and should also be considered in pediatric trials under certain circumstances. This allows patients to continue to derive benefit while isolated/oligometastatic disease can be managed with

other modalities, and longer-term assessments of clinical benefit, safety, and toxicity data can be conducted.

5.3 Inclusion of Children in Adult Trials

Clinical trials in children with cancer are often undertaken only during the late stages or following completion of adult trials. In specific indications and under certain conditions, it may be appropriate to enroll children in early- and late-phase adult clinical trials [14, 63, 88]. The FDA recently issued guidance on the inclusion of adolescents in adult oncology clinical trials [89]. There are several benefits to opening adult clinical trials to adolescents, including confirmation of a drug's MoA, a better understanding of drug biology, and obviating the need to recruit for a separate trial in adolescents [14].

For early-stage trials, once sufficient data from adults are available with regards to dose and toxicity, enrollment of children in phase 1 can be considered. Staged enrollment beginning with the cohort closest in age to adults (12–17 years) may be appropriate [63]. For later-stage trials, in the absence of adverse events indicated by nonclinical or early clinical data, the similarity in drug metabolism and excretion between adults and post-pubertal adolescents provides a rationale for inclusion of children aged ≥ 12 years in adult trials [63]. For pediatric cancers that also occur in young adults, it may be appropriate to include older pediatric patients (aged ≥ 12 years or post-pubertal patients, for example) in trials with young adults, especially given the similarity in metabolism/exposures between the two groups. Such an approach may be appropriate for cancers such as fibrolamellar hepatocellular carcinoma, which is a primary liver cancer that largely affects adolescents and young adults, with the largest number of patients being diagnosed at the age of 21 and the majority of patients diagnosed between 5 and 40 years of age [90].

Regardless of the strategy used for enrollment of pediatric patients, early involvement of both adult and pediatric oncologists in drug development/trial design is critical [14, 88, 91]. In addition, researchers need to ensure that validated, age-appropriate pediatric PRO measures are used for the pediatric patients in the trial, in order to accurately evaluate treatment experience from the pediatric perspective [36]. Lastly, an adequate number of pediatric cancer sites should also be included in the study.

6 Conclusions

In an effort to address the significant unmet need for more effective therapeutics in pediatric cancer, regulatory authorities in the US and EU have enacted legislation to accelerate the development of pediatric drugs. In order to comply, sponsors will need to consider studies in a pediatric population in concert with their adult drug development programs. Compared with clinical studies in adults, the specific needs of a pediatric population may require changes in assessment of preclinical rationale, translational relevance, formulation development, PK/PD, clinical endpoints, and trial design. Careful consideration of these factors will hopefully increase the likelihood of expeditiously delivering new therapeutics for pediatric cancer patients.

Declarations

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