Accelerating Drug Development in Pediatric Oncology With the Clinical Pharmacology Storehouse

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Abstract
Pediatric drug development is a challenging process due to the rarity of the population, the need to meet regulatory requirements across the globe, the associated uncertainty in extrapolating data from adults, the paucity of validated biomarkers, and the lack of systematic testing of drugs in pediatric patients. In oncology, pediatric drug development has additional challenges that have historically delayed availability of safe and effective medicines for children. In particular, the traditional approach to pediatric oncology drug development involves conducting phase 1 studies in children once the drug has been characterized and in some cases approved for use in adults. The objective of this article is to describe clinical pharmacology factors that influence pediatric oncology trial design and execution and to highlight efficient approaches for designing and expediting oncology drug development in children. The topics highlighted in this article include (1) study design considerations, (2) updated dosing approaches, (3) ways to overcome the significant biopharmaceutical challenges unique to the oncology pediatric population, and (4) use of data analysis strategies for extrapolating data from adults, with case studies. Finally, suggestions for ways to use clinical pharmacology approaches to accelerate pediatric oncology drug development are provided.

Keywords
clinical pharmacology, drug development, modeling and simulation, oncology, pediatric, PK/PD

Although pharmaceutical companies strive to be first-in-class for adult oncology indications, they almost never do so in pediatrics due to the rarity of these cancers and the difficulty in enrolling meaningful numbers of pediatric patients in the clinical trials. Worldwide, the number of drugs that have been studied in children and young adults has grown due to regulatory legislation increasing the transparency and accountability of pediatric drug development.¹ There are available mechanisms for seeking formal or informal advice from the regulatory agencies such as at the pre-investigational new drug stage through discussions with the US Food and Drug Administration’s (FDA) Office of Clinical Pharmacology, Office of New Drugs for pediatrics, pediatric Oncology Drug Advisory committee, international collaboration initiative by the Office of Pediatric Therapeutics, and the European Medicine Agency’s (EMA) Paediatric Committee. However, the pathways by which regulatory approval of pediatric studies is sought differ with respect to scope and timing. This lack of alignment may hamper and/or delay global approaches to pediatric drug development. Since 2002, results of pediatric studies have been added to the labels of 34 cancer drugs,²³ of which 15 have approved pediatric indications (Table 1). Despite this progress, there are still more opportunities to increase the number of drugs available to children and to speed their availability. A recent review of molecularly targeted oncology drugs suggested that studies in pediatrics based on molecular mechanism of action, rather than indication, may accelerate drug development in pediatrics.¹ For prescribers and patients, information on the use of drugs in children may not be available until several years after the initial approval in adults,³ leading to substantial off-label drug use in the pediatric population. New strategies for designing and conducting clinical trials have emerged to overcome challenges associated with conducting studies in children. Perhaps one of the greatest challenges for drug developers is the lack

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| Trade Name (Generic Name) | Pediatric Labeling Date | Pediatric Indication(s) | Pediatric Dosing Regimen and Supporting Evidence | Adult Indication(s) | Adult Dosing Regimen | S/H | Was Efficacy in Children Similar to Adults? (Per Approved Label) |
|--------------------------|-------------------------|-------------------------|--------------------------------------------------|---------------------|---------------------|-----|----------------------------------------------------------------|
| Arranon (nelarabine)     | 10/2005                 | T-cell ALL; T-cell lymphoblastic lymphoma (age range studied: 2.5-21.7 years) | 650 mg/m² IV over 1 hour daily for 5 consecutive days repeated every 21 days; based on 1 clinical trial in pediatric patients | T-cell ALL and T-cell lymphoblastic lymphoma | 1500 mg/m² IV over 2 hours on days 1, 3, and 5 repeated every 21 days | H   | Yes; based on complete response data |
| Afinitor (everolimus)    | 10/2010 and 8/2012      | Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis in patients ≥3 years of age | 4.5 mg/m² orally QD; adjust dose to attain trough concentrations of 5-15 ng/mL; based on 1 clinical trial in pediatric | Advanced hormone receptor-positive, HER2-negative breast cancer; progressive neuroendocrine tumors; advanced renal cell carcinoma; renal angiomylipoma and tuberous sclerosis complex; SEGA | 10 mg orally QD | S   | Yes; for SEGA based on 1 trial with pediatrics and young adults patients |
| Bavencio (avelumab)      | 3/2017                  | Metastatic MCC in patients aged ≥12 years | 10 mg/kg IV over 60 minutes every 2 weeks; based on several clinical trials in adult patients and population pharmacokinetics data to support use in pediatric patients aged ≥12 years | Metastatic MCC | Same as pediatric | S   | Yes; based on full extrapolation from adults using population pharmacokinetics data and assuming the course of MCC is sufficiently similar in adults and pediatric patients |
| Blincyto (blinatumomab)  | 8/2016                  | B-cell precursor ALL in first or second complete remission with MRD ≥0.1%; R/R B-cell precursor ALL (age range studied: <1-17 years) | Cycle 1 dosing (all doses IV) MRD positive: Weight ≥45 kg: 28 μg/day for 28 days Weight <45 kg: 15 μg/m²/day, not to exceed 28 μg/day, for 28 days R/R: Weight ≥45 kg: 9 μg/day for 7 days, 28 μg/day for 21 days Weight <45 kg: 5 μg/m²/day, not to exceed 9 μg/day, for 7 days, 15 μg/m²/day, not to exceed 28 μg/day, for 21 days Based on limited experience in 41 pediatric patients in a dose-escalation study | B-cell precursor ALL in first or second complete remission with MRD ≥0.1% or R/R B-cell precursor ALL | Based on weight; same as pediatric | H   | Yes; based on partial extrapolation from adults with MRD-positive B-cell precursor ALL |
| Busulfex (busulfan)      | 1/2003                  | Part of a conditioning regimen in hematopoietic stem cell transplant (age range studied: 5 months to 16 years) | Part of a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplant for CML | Part of a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplant for CML | 0.8 mg/kg of ideal body weight or actual body weight as a 2-hour IV infusion every 6 hours for 4 consecutive days for a total of 16 doses | H   | Yes; based on full extrapolation from adult CML |

(Continued)
| Trade Name | Pediatric Labeling Date | Pediatric Indication(s) | Pediatric Dosing Regimen and Supporting Evidence | Adult Indication(s) | Adult Dosing Regimen | S/H | Was Efficacy in Children Similar to Adults? (Per ApprovedLabel) |
|------------|-------------------------|--------------------------|-------------------------------------------------|---------------------|---------------------|-----|-------------------------------------------------|
| Clolar (clofarabine) | 12/2004 | R/R ALL in patients aged 1-21 years | 52 mg/m² IV over 2 hours daily for 5 consecutive days of a 28-day cycle; based on one clinical trial in R/R ALL in pediatrics and young adults | NA | NA | H | Yes; based on data in pediatrics and young adults in R/R ALL |
| Erwinaze (asparaginase Erwinia chrysantheni) | 11/2011 | ALL in patients with hypersensitivity to E. coli-derived asparaginase (age range studied: 2–18, 1-17, and 0-76 years) | 25,000 IU/m² IM or IV 3 times a week; based on 2 clinical trials in pediatric patients | NA | NA | H | Efficacy not established in adults |
| Gleevec (imatinib mesylate) | 9/2006 | Newly diagnosed Ph+ CML in chronic phase; Ph+ acute ALL (age range studied: ≥ 1 year) | 340 mg/m²/day orally QD (not to exceed 600 mg) for Ph+ CML or Ph+ ALL or as a split dose in the morning and evening for Ph+ CML; based on several clinical trials in pediatric patients | Ph+ CML; Ph+ ALL; myelodysplastic/myeloproliferative diseases; aggressive systemic mastocytosis; hypereosinophilic syndrome and/or chronic eosinophilic leukemia; dermatofibrosarcoma protuberans; malignant gastrointestinal stromal tumors | 400-800 mg orally QD depending upon the indication | H | Yes; based on complete cytogenic response rate for Ph+ CML in chronic phase. Ph+ acute ALL used a different end point relative to adults |
| Keytruda (pembrolizumab) | 11/2017 | Refractory cHL; refractory PMBCL; unresectable or metastatic MSI-H or mismatch repair deficient solid tumors; colorectal cancer (age range studied: 2-18 years) | 2 mg/kg (up to 200 mg) IV every 3 weeks; based on limited clinical studies in pediatric patients and extrapolation from several studies in adults | Melanoma; NSCLC; HNSCC; classical Hodgkin lymphoma, PMBCL; urothelial carcinoma; microsatellite instability-high cancer; gastric cancer; cervical cancer | 200 mg IV over 30 minutes every 3 weeks | S/H | Yes; based on full extrapolation from adults data in cHL, PMBCL and MSI-H |
| Kymriah (tisagenlecleucel) | 8/2017 | B-cell precursor ALL refractory or in second or later relapse in patients aged ≤ 25 years | Weight ≤ 50 kg: 0.2-5.0 × 10⁶ CAR-positive viable T cells per kg body weight administered IV Weight > 50 kg: 0.1-2.5 × 10⁶ total CAR-positive viable T cells (non-weight based) administered IV; based on 1 clinical trial in pediatrics and young adults | B-cell ALL (young adults); R/R DLBCL after 2+ lines of systemic therapy | 0.6 to 6.0 × 10⁶ CAR-positive viable T cells administered IV (R/R DLBCL) | H | Yes; based on CR rate in r/r B-cell ALL |
| Mylotarg (gemtuzumab ozogamicin) | 9/2017 | R/R CD33+ AML in patients aged ≥ 2 years | 3 mg/m² (up to one 4.5 mg vial) IV on days 1, 4 and 7; based on 1 clinical trial in pediatric r/r AML patients | Newly diagnosed or R/R CD33+ AML | 3 mg/m² (up to one 4.5 mg vial) IV on days 1, 4, and 7 in combination with daunorubicin and cytarabine; 6 mg/m² IV on day 1 and 3 mg/m² on day 8 as a single agent | H | Yes; based on CR rates in r/r AML pediatric and young adults |
| Trade Name (Generic Name) | Pediatric Labeling Date | Pediatric Indication(s) | Pediatric Dosing Regimen and Supporting Evidence | Adult Indication(s) | Adult Dosing Regimen | S/H | Was Efficacy in Children Similar to Adults? (Per Approved Label) |
|--------------------------|-------------------------|-------------------------|--------------------------------------------------|---------------------|----------------------|-----|----------------------------------------------------------|
| Sprycel (dasatinib)      | 11/2017                 | Ph+ CML in chronic phase (age range studied: ≥ 1 year) | Starting dose of 40-100 mg orally QD based on body weight; tablet dosing not recommended in patients weighing <10 kg; based on 2 clinical trials in pediatric patients with chronic-phase CML | Newly diagnosed Ph+ CML in chronic phase; chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML resistant or intolerant to prior therapy including imatinib; Ph+ chromosome-positive ALL with resistance or intolerance to prior therapy | Starting dose of 100-140 mg orally QD | H   | Higher efficacy in pediatrics based on comparison of complete cytogenetic response rates within 12 months |
| Tasigna (nilotinib)      | 3/2018                  | Newly diagnosed Ph+ CML in chronic phase or newly diagnosed Ph+ CML in chronic phase resistant or intolerant to prior TKI therapy in patients aged ≥ 1 year | 230 mg/m² orally BID, rounded to the nearest 50-mg dose (to a maximum single dose of 400 mg); based on two clinical trials in pediatric patients | Newly diagnosed Ph+ CML in chronic phase; chronic phase and accelerated phase Ph+ CML resistant/intolerant to prior therapy including imatinib | 300-400 mg orally BID | H   | Yes; for newly diagnosed Ph+ CML |
| Unituxin (dinutuximab)   | 3/2015                  | High-risk neuroblastoma (in combination with GM-CSF, IL-2, and 13-cis-retinoic acid) (age range studied: 11 months to 18 years) | 17.5 mg/m²/day IV over 10-20 hours for 4 consecutive days for up to 5 cycles; based on 1 clinical trial in pediatric patients | NA | NA | S   | Efficacy not established in adults; neuroblastoma is a pediatric-specific cancer |
| Xgeva (denosumab)        | 6/2013                  | Giant cell tumor of bone in skeletally mature adolescents (age range studied: 13-17 years) | 120 mg SC every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy; based on one clinical trial in adolescent patients. | Prevention of skeletal-related events in patients with MM and patients with bone metastases from solid tumors; giant cell tumor of bone | 120 mg SC every 4 weeks; 120 mg SC every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy for patients with giant cell tumor of bone | S   | Yes; based on efficacy in skeletally mature adolescents and adults |

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BID, twice daily; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CML, chronic myelogenous leukemia; DLBCL, diffuse large B-cell lymphoma; GM-CSF, granulocyte-macrophage colony stimulating factor; HER2, human epidermal growth factor receptor 2; HNSCC; head and neck squamous cell carcinoma; IL-2, interleukin-2; IM, intramuscular; IV, intravenous; MCC, Merkel cell carcinoma; MM, multiple myeloma; MRD, minimal residual disease; MSI-H, microsatellite instability-high; NA, not applicable; NSCLC, non–small cell lung cancer; Ph+, Philadelphia chromosome positive; PMBCL, primary mediastinal B-cell lymphoma; QD, once daily; R/R, relapsed or refractory; SC, subcutaneous; S/H, solid tumor or hematological malignancy; TKI, tyrosine kinase inhibitor.

*Based on US FDA approvals obtained since 2002 (adapted from FDA2,3). The indications and dosing regimens have been summarized for brevity; consult approved labeling for complete descriptions of indications and dosing regimens.
of empirical data in the target population that can be used to inform the initial dose, particularly for oncology drugs. Problems with dose selection and trial design in pediatric oncology drug development, where new drugs are often added to existing treatment regimens, complicates data interpretation and can then lead to high rates of clinical trial failure, delaying patients’ access to potentially effective treatments.

In a concept paper issued in 2017, the EMA recognized that a revision of the guideline on the role of pharmacokinetics (PK) in pediatric drug development is needed to address recent advances in the field and to take into account new knowledge that has been gained as a result of the pediatric regulation coming into force. The FDA and the EMA have also issued guidance documents supporting the use of quantitative clinical pharmacology modeling and simulation analyses in pediatric drug development. These documents plus several subsequent concept papers and addenda outline considerations for the use of quantitative approaches in pediatric drug development, which have aided drug developers in applying these approaches. The aim of the current work is to summarize the role of clinical pharmacology approaches in pediatric drug development with a specific focus on the challenges encountered in pediatric oncology drug development (Figure 1). The examples described herein are intended to highlight practical considerations for implementing the clinical pharmacology approaches described in the regulatory guidances.

**Clinical Pharmacology Considerations**

**Study Plan**

**Overall Timeline.** Pediatric studies lag behind adult studies primarily because of the rarity in the population. Assuming that a compound is expected to be effective in a common cancer and a rare cancer, sponsors would typically choose to conduct clinical trials for the common cancer because of enrollment efficiencies as well as economic advantages. In Europe, the regulatory requirement is to have a pediatric investigational program in place at the end of the phase 1 trial. In the United States, the requirement for a pediatric study plan is at the end of phase 2.

Even more problematic is the fact that adults, adolescents, and younger children often do not have the same cancer disease types. Of the 10 most common cancer types, only non-Hodgkin lymphoma occurs in all 3 age groups, and even then, the prevalent histologic subtypes in children differ greatly from those in adults. Because all pediatric solid tumors and lymphoid malignances are rare, dedicated development of drugs for a pediatric indication are limited, with the exception of drugs for neuroblastoma.

Concerns about lack of long-term safety data before enrolling children in clinical trials early are warranted. Preclinical toxicology studies are not able to address these concerns. However, utilizing the argument that children should not be treated until the long-term effects are known would delay pediatric development and access to therapies in a timely fashion. In a recent analysis of 25 molecularly targeted agents approved by the FDA or EMA for adult cancers and evaluated in pediatric cancers, the toxicities in children associated with 24 drugs were usually similar as those observed in adult patients, with the main PK parameters being comparable as well, except for drugs with a narrow therapeutic index. Another review of nononcology drugs for pediatrics concluded that the observed toxicities may not be predicted in children based exclusively on adults. In the context of unknown long-term side effects, the patient and the treating physician must make a decision based on potential benefits associated with response, compared to unknown or suspected long-term consequences. For these reasons, accelerating drug development in children could be achieved by allowing adolescents to enroll into adult clinical trials and first-in-human phase 1 studies. Subsequently, children can be enrolled after the initial dose escalation phase in adults is completed, once a maximum tolerated dose or...
recommended phase 2 dose has been identified, and the adult equivalent doses for children are estimated.

**Study Design.** From a clinical pharmacology point of view, characterization of PK and the PK/PD relationship to determine the optimal dose are primary objectives. The PK and PK/PD relationships are typically characterized in early studies and then confirmed in late-stage studies.

Oncology phase 1 trials typically include a dose-escalation phase and dose-expansion phase. The objective of the dose-escalation phase is to characterize the PK and safety in adult subjects. Studies in pediatric subjects are typically conducted after a therapeutic dose has been determined. If the disease progression and PK/PD relationship can be expected to be similar between pediatric subjects and adults, then an initial cohort of subjects for PK characterization to select a dose that provides similar exposure to the adult therapeutic dose can be followed by a larger expansion cohort, without evaluation of multiple doses. This is especially true for targeted therapies that do not have a narrow therapeutic index and tend to have better safety profiles compared to cytotoxic drugs. An example of this approach is the proposed design for a nivolumab pediatric study in which the target adult dose of 3 mg/kg is the only dose that is being proposed with an option to go to a lower dose if needed.\(^\text{18}\) For combination with ipilimumab, a single dose of nivolumab with 2 doses of ipilimumab is being proposed.\(^\text{18}\) The venetoclax pediatric study is designed similarly, with the initial pediatric subjects receiving an age- and weight-adjusted dose to match the adult plasma exposure at the target dose of 800 mg daily for adult patients with acute myeloid leukemia and multiple myeloma. The lack of serious toxicities related to venetoclax and the relatively wide therapeutic window allowed for the use of this starting dose strategy in the dose determination portion of the pediatric study.\(^\text{19}\)

Another challenge in pediatric phase 1 trials in which PK characterization is the primary objective is the inclusion of a wide variety of tumor types and age ranges (neonates to <18 years), due to the rarity of pediatric cancers in general, making up less than 1% of all cancers diagnosed each year. Because these trials typically enroll a small number of subjects for each dose group (eg, 3-6) due to typical statistical designs, characterizing the PK across the age range and tumor spectrum is difficult. The above-mentioned approach of limiting the initial or dose-escalation cohort to 1 or 2 doses allows enrollment of sufficient numbers of subjects across age ranges to provide a better understanding of PK comparability to the adult population.

If the assumptions of disease similarity cannot be reasonably made, which is often the case in pediatric cancers in which the disease is not attributed to factors that play a role in disease progression or initiation in adults (ie, environmental or lifestyle factors), a more extensive program for PK characterization and dose finding may be required prior to conducting the confirmatory safety and efficacy studies. While typical study designs like the 3+3\(^\text{20}\) or rolling 6\(^\text{21}\) are commonly used for dose escalation, Bayesian designs like the continual reassessment method\(^\text{21,22}\) or adaptive logistic regression\(^\text{23}\) design may be preferable and should be considered in pediatric studies. In the case where the toxicity profile of the drug has been characterized in adult subjects, the continual reassessment method design might be more appropriate than the 3+3 design in pediatric studies. An extensive review of pediatric dose-finding studies showed that for approximately 75% of the molecularly targeted agents studied, the pediatric recommended phase 2 dose was very similar (90%-130% of the adult recommended phase 2 dose) to the FDA-approved dose in adults.\(^\text{15}\) For the dose-expansion phase, an adaptive and Bayesian design can be employed to ensure that an unnecessarily large number of subjects are not exposed to a drug that does not show therapeutic benefit. The Bayesian optimal interval design is one such method that is being proposed in the dose-expansion phase of venetoclax pediatric trials.\(^\text{19,24}\)

Another design for including younger children in first-in-human phase 1 oncology trials is to begin with dose escalation in adults. If a maximum tolerated dose has not been reached, then it would be feasible to open an expansion cohort of children to be dosed at the same recommended phase 2 dose as adults. If a maximum tolerated dose was reached, then dosing in children could begin at approximately 80% of the adult dose, or at the next lower tested dose level, followed by dose escalation if tolerated and assuming the administered dose will provide exposure equivalent to target exposure in adult patients. Starting at 80% increases the likelihood that the patient will benefit, as it is close to the adult dose, but it does presume that children will have a similar threshold for toxicity as adults.\(^\text{25}\) A dose lower than 80% or dose similar to adults should also be considered based on the available exposure-response data and clinical profile of the drug. The ability to eliminate lower dose levels also minimizes the number of children required for the study. Exceptions to this paradigm may include drugs with a narrow therapeutic index, drugs with suspected differences in the volume of distribution between adults and children, and drugs for infants (ages 28 days to 2 years), where a more traditional escalation schedule with an emphasis on safety and PK assessments should be considered. These recommendations are similar to those endorsed by the Innovative Therapies for Children with Cancer Consortium in the European Union.\(^\text{14}\)
**Age Groups.** Many physiologic characteristics are shared between older children and adults; for example, children 12 years of age and older have the same percentages of total body water, extracellular fluid, and intracellular fluid and the same creatinine clearance as adults. This suggests that the volume of distribution of drugs will be similar for children 12 years of age and older compared with adults. The drug-metabolizing isoenzymes in the liver and intestine are immature at birth and mature over time, ranging from 2 years for cytochrome P450 (CYP) 3A to 12 years for CYP2D6 to reach full maturation. Therefore, by the age of 12, all isoenzymes have reached the adult levels, leading to similar drug clearance. Thus, from a PK perspective, no difference would be expected between adolescents 12 to 17 years of age and adults. A cross-functional analysis by multiple departments at AbbVie found that there were no absolute contraindications from a scientific or medical perspective to enrolling adolescents in oncology adult clinical trials, for the same indication. AbbVie Oncology has thus implemented a new strategy whereby oncology protocols, including first-in-human phase 1 adult trials that may be relevant to the adolescent population, will have age inclusion criteria of ≥12 years of age. This strategy has also been endorsed by the American Society of Clinical Oncology/Friends of Cancer Research, the Innovative Therapies for Children with Cancer, and more recently by the FDA.

The paradigm for younger children is different. Additional concerns for this age group include developmental factors that lead to different volumes of distribution, organ maturation, drug-metabolizing enzyme and transporter ontogeny for small molecules, maturity of catabolizing enzymes and receptor-mediated endocytosis for large molecules, inability to swallow pills and need for a suitable age-appropriate formulation, and the desire to avoid exposure to subtherapeutic doses. Study design considerations that were highlighted in the previous section are suggested to account for some of these factors.

**Pharmacokinetic/Pharmacodynamic Sample Acquisition.** There are presently no clear global guidelines on the limits of blood volume and frequency of blood draws for children of various ages. A typical intensive blood-sampling schema to establish a PK/PD profile in adults may not be achievable in children, due to limits on maximum of blood volume drawn in a given time period (and equally the lack of universal guidelines for blood collection), ability to draw blood samples during hospitalization vs a clinical visit, and compliance (especially for very young children or infants) where multiple needle pricks are applied per visit to collect the required multiple samples. In pediatric oncology patients, who may be suffering from hematologic malignancies or toxicities due to chemotherapy, the bone marrow dysfunction can inhibit erythropoiesis and shorten red cell survival, thereby reducing the body’s ability to replenish the blood taken through sampling. These disease factors impose limitations on the amount and number of blood samples to be taken from pediatric oncology patients. Therefore, it is recommended to minimize the number of blood draws for PK/PD sampling, without compromising the quality of the collected data, in order to avoid additional burden on pediatric cancer patients.

A useful survey by Altamimi et al found that across age groups there was no difference in the collected volume per sample or per child, while a significant difference was found in the frequency of sampling between sparse PK sampling (also known as population PK) and traditional intensive PK sampling studies in children. This suggests that clinical pharmacologists should emphasize the use of population-based approaches to optimize the blood collection time-points to avoid the limitations described above. It can be further argued that it is an ethical responsibility for sponsors and in particular clinical pharmacologists to use modern population PK approaches that optimize the PK/PD sampling schema by minimizing the number of samples needed while maintaining quality of the collected PK/PD information, with the objective of minimizing the patients’ burden in this special population. As shown by Wade et al, population PK modeling can allow sparse PK sampling in the pediatric population. Suyagh et al employed dried blood spotting, a microvolume sampling technique to analyze PK of metronidazole in neonates. Collectively, these clinical pharmacology approaches should be utilized to minimize collection of frequent samples while ensuring optimal design for collecting necessary information and data in the pediatric oncology population.

**Dosing**

**Starting Dose Projections.** Historically, the starting dose for pediatric oncology phase 1 studies was generally based on the adult dose adjusted for body size, and mostly based on body surface area. This approach was implemented during the era of cytotoxic drug development, where the aim was to minimize toxicity among pediatric patients by correcting for body surface area. Although this approach is still used in clinical practice (ie, chemotherapy dosing) and may still be appropriate for large-molecule drugs (ie, monoclonal antibody therapeutics), it is almost abandoned for newer targeted oral therapies due to the lack of scientific evidence and justification for body size–adjusted dosing.
eral approaches for conducting pediatric clinical stud-

Considerations for Pediatric Studies recommends sev-

The FDA guidance for General Clinical Pharmacology

ing is used to predict exposures in pediatric subjects.

Although general PK principles apply
to both small-molecule and large-molecule biologics,
the underlying mechanisms that affect absorption,
distribution, metabolism, and excretion are quite
different between these 2 modalities. Therefore, develop-
mental changes in pediatrics (ie, total body water,
catabolic enzymes, receptor-mediated endocytosis, and
fat content) must also be accounted for when large-
molecule doses are evaluated for pediatric patients,
especially when simple body size adjustment relative to
adults may not offer optimal dosing in children.

From a practical point of view, fixed flat dosing is
recommended for oral, targeted drugs to preclude the
need for body size normalization and dosing errors,
especially in the infant group where accurate determi-
nation of body surface area may not be possible. For
large molecules, an attempt to develop flat fixed dosing
per age or body size group would be advantageous if
warranted, to avoid dosing errors in small patients.

The disease similarity or difference between adult
and pediatric patients dictates the ability for extrapo-
lation of efficacy and hence the selection of an effica-
cious starting dose. For pediatric oncology studies, it
is not feasible to study a range of doses where a dose
may be subtherapeutic due to ethical considerations.
This presents an opportunity for using modeling and
simulation to select a starting pediatric dose, for exam-
ple, based on an understanding of exposure-response
relationships in adults and matching target exposures in
children after accounting for factors that influence the
PK, assuming the relationship in adults and children is
sufficiently similar. For example, in case of venetoclax,
the initial target dose was selected to be an adult ex-
sure equivalent of 800 mg daily. The 800 mg daily adult
dose was selected based on safety and efficacy data of
venetoclax available in adults with various hematologic
malignancies. The pediatric target dose was weight or
age adjusted, taking into consideration the maturation of
CYP3A4, which metabolizes venetoclax. Another
commonly used approach for pediatric starting dose
determination is physiologically based pharmacokinetics
(PBPK) modeling and simulation. Rioux and Waters
have discussed several examples where PBPK model-
ing is used to predict exposures in pediatric subjects.

Pediatric Formulations. When the pediatric require-
ments went into effect, not enough attention and effort
was devoted to developing age-appropriate formul-
ations. In many instances, extemporaneous formulations
were prepared at home by grinding the adult dosage
form and suspending it in an appropriate liquid vehicle.
This created dosing and administration problems as
well as stability issues. Since then, most regulatory
authorities require age-appropriate formulations that
do not restrict dosing flexibility or present palatability
or dosing issues and that would be stable over the
duration of treatment. As a consequence, most drug
companies embarked on extensive pediatric formula-
lation development efforts that required the conduct of
in vivo studies, usually in healthy adult volunteers. It
was assumed that if the formulations were found to be
bioequivalent in adults, then they were assumed to be
bioequivalent in the target pediatric population. Close
attention should be paid to the choice of excipients
used in the pediatric formulations, particularly liquid
formulations. For example, it is well known that sorbitol
and most other sugar alcohols can have a profound
effect on absorption and bioavailability. Sorbitol and
alcoholic sugars can increase gastrointestinal fluid vol-
ume, leading to reduced small intestinal transit time.
Consequently, the decreased bioavailability could result

ies and extrapolation algorithms. Because pediatric
oncology indications are mostly unique and dissimi-
lar to the disease in adults (ie, disease progression
is not similar to adults), full or partial extrapolation
approaches based on PK and PK/PD are generally not
possible and the pediatric study objectives would focus
on providing evidence of effectiveness and safety and
to characterize the PK and exposure-response relation-
ships in pediatric oncology patients to enable optimal
dosing. Understanding of tumor biology and markers
disease in pediatric patients along with bridging of
knowledge from trials in adult patients may offer more
opportunity to inform pediatric clinical trials. Despite
these challenges, an analysis of the labels of 34 cancer
drugs in Table 1 where the pediatric cancer was evalu-
ated in adults (except for conditions that are exclusively
in pediatrics only) revealed that after correcting for
body size (mg/kg or mg/m²), for approximately 50% of
these drugs the pediatric and adult doses were the
same, 13% were within 70% to 130% of the adult dose,
20% had a higher adult dose (≥50%), and 20% did
not have an adult dose (due to condition existing only
in pediatrics, such as neuroblastoma) for comparison
(Figure 2). Overall, the majority of cancer drugs had
similar body size–adjusted pediatric and adult doses on
their labels.

Biopharmaceutical Considerations.

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and pediatric patients dictates the ability for extrapo-
lolation of efficacy and hence the selection of an effica-
cious starting dose. For pediatric oncology studies, it
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in decreased efficacy in certain pediatric age groups, necessitating an increase in dose to match the adult doses, as was the case with the lamivudine oral solution dosage form, where the dose was increased by 25%. Moreover, development of formulations for oncology indications can present unique challenges in that in many instances the drugs cannot be tested in healthy volunteers due to toxicity issues. Despite these issues, the assessment of relative bioavailability and palatability of the pediatric formulations is typically performed in adults to have a general idea on the exposure achieved with these formulations and, if needed, adjust the dose to be given to the pediatric population.

Effect of Food on Bioavailability in Children. Lipophilic drugs with poor bioavailability formulated in such a way that they are always given with food pose a particular challenge. Because the adult diet could be somewhat different and the fact that pediatric oncology patients may not eat full meals or might be on a specific diet due to their illness, it is not possible to achieve the full exposure levels that are achieved with adults in the fed state. For all the above considerations, formulations that need to always be given with food should be avoided. However, it might be possible to overcome this challenge by formulating the drug as sprinkles or mini-tablets that can be dispersed in a vehicle such as apple sauce, yogurt, or a vehicle that is suitable for children. The bioequivalence or at least the establishment that the exposure levels obtained from such a mode of administration are sufficiently similar to those achieved by the formulation used in the clinical trials is a prerequisite to the acceptability of such an approach.

Extrapolation of Drug-Drug Interactions From Adults. Because it may be unethical and infeasible to conduct drug-drug interaction (DDI) trials in pediatrics in general and in oncology patients in particular, drug interaction results in adults are typically extrapolated to pediatrics based on the dosing considerations described above (ie, intrinsic factors that influence drug clearance). However, due to known physiologic and developmental differences between adults and children (ie, drug-metabolizing enzyme ontogeny), DDIs are often extrapolated using modeling and simulation approaches such as PBPK, when the ontogeny of drug elimination pathways is well understood such as in the case of CYP3A-mediated metabolism. Not only does this provide a more scientifically robust approach to provide DDI recommendations and dose adjustment in children, but it also provides a platform to simulate scenarios that are otherwise impossible to test clinically and ethically. Furthermore, some chemotherapy regimens differ even when the disease type is the same in children and adults, often due to the inability of older adults to tolerate a more intensive regimen (ie, PEG-L-asparaginase is always used in pediatric acute lymphocytic leukemia protocols but rarely in adult protocols). Therefore, DDI information on such combinations would be completely absent. It also may be impossible to adjust the chemotherapy dose (ie, lower dose/intensity) when introducing the new drug if DDI is suspected, since the new drug may not provide efficacy and the loss of benefit to the child from adjusting backbone therapy would leave the patients in a subtherapeutic window. This again highlights the need for a model-informed drug development approach to provide the appropriate dosing instructions for concomitant drug administration in children. Kersting et al developed a PBPK model for etoposide using data from adult patients and successfully scaled it down to predict plasma concentrations in children. Comedications impacting the metabolism and excretion of etoposide were also taken into consideration in this model to inform dosing in children. Overall, simulated and observed plasma concentration-time profiles were in agreement for different age groups. This PBPK approach presents an opportunity for quantitative pharmacology to improve study designs and dosing, where DDI data from adults are absent and thus extrapolation of DDI to children would not be possible, considering that the ontogeny of drug elimination pathways are well understood.

Data Analysis and Modeling
Data analysis and modeling strategies need to be aligned with the major objectives of the study, which are informed by the pediatric study decision tree. Generally, there appear to be 3 major objectives for
PK Bridging. For this type of study, modeling and simulation can help inform the starting dose, dose regimen optimization, and optimization of the study design. PBPK and allometry represent the most common scaling approaches to leverage available PK data from adult oncology patients to help define pediatric doses and regimens. The selection of the appropriate methodology is a function of the age range to be studied in the trial. Allometric approaches may not work well for very young children where age-dependent enzyme and transporter function may alter drug elimination; however, when enough data are available to empirically determine the allometric age-dependent exponents in the pediatric population for the relevant PK parameters, allometry may provide similar results in the young children group compared to PBPK. Summaries of the pediatric dosing regimens for cancer drugs with an FDA-approved pediatric indication obtained since 2002 and comparisons to the dosing regimens in adults are shown in Table 1.

Key applications of PBPK modeling include support for the first pediatric trial, starting dose selection, prediction of drug exposures across the age continuum, optimization of blood sample collection, prediction of target organ exposure, and evaluation of the drug interaction potential. There are a number of retrospective examples to show the utility of the approach, and prospective examples in pediatric oncology are beginning to emerge. Thai et al developed a PBPK model for docetaxel, incorporating in vitro absorption, distribution, metabolism, and excretion and intravenous PK data from over 500 cancer patients after either single or multiple dosing to optimize dose and sampling times for a pediatric PK bridging study. The model appropriately predicted docetaxel plasma concentration-time profiles in neonates to 18-year-old patients. Challenges and limitations associated with the application of PBPK modeling in pediatrics include the lack of complete information on drug absorption processes, drug-metabolizing enzymes, and transporters. In addition, as highlighted by the example for docetaxel, the PBPK approach tended to under-predict the intersubject variability in drug exposure, highlighting an additional challenge in defining variability in ontogeny functions in pediatrics. It will be important to continue to accrue examples of prospective DDI predictions in pediatrics given the role of combination drug therapies in attaining successful patient outcomes.

For study design optimization, it is necessary to use population PK approaches to define sparse sampling schedules to minimize blood volume collection and maximize the value of PK data collection in pediatric oncology patients due to the challenges described in the previous section on dosing. In addition, these approaches can help inform sample size for sufficient precision of PK parameters.

Pharmacokinetic/Pharmacodynamic Studies. The main objective of PK/PD studies is to characterize the relationship between exposure and pharmacodynamic end points in cases in which a difference between adult and pediatric patients is suspected. A key challenge for oncology in general revolves around the development and validation of PD end points to characterize target engagement and/or pathway modulation required to provide support for optimal dose and regimen selection. One general paradigm involves the use of longitudinal tumor volume measurements and their ability to predict outcomes such as progression-free survival or overall survival. For tumors that arise predominantly in a pediatric population (ie, Wilms or neuroblastoma), there is limited opportunity to validate the translational value of a PD end point to inform drug development and further emphasizes the need for dedicated pediatric studies in cancers that affect only children to further inform translational value of PD end points.

In oncology, biomarkers are frequently used to identify subsets of patients with a greater chance of responding to a particular therapy. The phase 1 study of crizotinib in pediatric patients highlights the importance of exploiting a known biomarker across a variety of adult and pediatric cancers. Crizotinib, an ALK inhibitor, has shown excellent response rates in chemotherapy-refractory non-small cell lung cancer (NSCLC) patients with anaplastic lymphoma kinase (ALK) translocations. The ALK oncogene is frequently mutated in patients with advanced neuroblastoma, and it is also commonly overexpressed in lung cancer, thyroid cancer, anaplastic large-cell lymphoma, rhabdomyosarcoma, and glioblastoma multiforme. In the phase 1 study in pediatric patients, for the dose-escalation part of the study, patients between the ages of 12 months and 22 years with solid or central nervous system tumors, anaplastic large-cell lymphoma, or any other cancers for which there is no known curative treatment were eligible to enroll. For the other 2 parts of the study, only patients with confirmed ALK translocations, mutations, or amplifications were enrolled. Currently, further clinical studies are under way in children with neuroblastoma and anaplastic large-cell lymphoma. Continuing to define the quantitative PK/PD relationships for biomarkers will aid in the ability to efficiently develop new treatments in pediatric patients by leveraging prior experience in adult populations.
Full Development Studies Including PK, Safety, and Efficacy.

Traditional exposure-efficacy and exposure-safety analyses can be used in conjunction with biomarker and safety data to support the proposed dosing regimen in pediatric oncology. Frequently, a dosing paradigm based on the maximum tolerated dose is selected for oncology therapeutics, necessitating a single dose level in safety and efficacy studies. Given that the range of drug exposures associated with a single dosing intensity is much smaller than the range achieved when an array of doses is selected, it may be challenging to extrapolate the results from a single dose level to other cases with different doses or regimens. Therefore, the goal of exposure-response analyses is to identify patients who are suboptimally exposed to the drug due to covariate factors. For example, the population PK of imatinib, a small molecule that inhibits the constitutive abnormal bcr-abl tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia, was characterized in a combined analysis including children and adults. Adult patients (n = 34; age ≥18 years) received oral imatinib 400 mg/day while children, adolescents, and young adults (n = 33; age <21 years) received oral imatinib 340 mg/m²/day with PK samples collected after the first dose and on days 30 and 60. A base population PK model adequately described the concentration-time profile of imatinib and its primary metabolite CGP74588 in children and adults. Body weight, alpha acid glycoprotein plasma level, and albuminemia were identified as covariates that influenced imatinib clearance, and inclusion of these covariates reduced the intersubject variability in clearance from 47% to 19%. Children had a slightly higher imatinib exposure compared to adults due to a higher dose (417 mg/day vs 400 mg/day) and lower clearance (6.2 L/h vs 8.22 L/h) in children and adults, respectively. This study illustrates the value of characterizing the PK properties in children and adults, and the significant impact that population PK/PD analyses provide in selecting the optimal dosages for pediatric oncology patients.

Conclusions and Recommendations

This work has highlighted the opportunities in which clinical pharmacology–based approaches can be (and arguably must be) used to overcome the challenges encountered in pediatric oncology drug development. In the past, pediatric studies have lagged behind adult studies due to the difficulty in enrolling sufficient numbers of pediatric patients and the lack of long-term safety data from adults. Moving forward, on the basis of scientific evidence where the disease, safety, PK, and dosages in adolescents were comparable to those in adults, it is recommended that adolescents be included in adult oncology clinical trials and/or first-in-patient studies to avoid the lag time that currently hinders pediatric drug development and access to useful therapies. Similarly, study designs can be modified and Bayesian methodologies and pediatric expansion cohorts can be employed to establish optimal doses in children sooner and with greater confidence, especially for targeted therapies. Because sample acquisition remains a concern and there are no clear guidelines on the frequency or volumes of sample collection in children of various ages, population-based PK analyses that use sparse PK sampling and optimized PK/PD sampling designs such as simulations or D-optimality approaches can significantly minimize excessive sampling in children, especially in cancer patients who suffer from hematologic deficiencies due to disease or chemotherapy. Establishing an optimal starting dose of a convenient, age-appropriate formulation remains important for successful pediatric oncology drug development. Use of modeling and simulation approaches must continue to advance to inform selection of safe and efficacious doses as early in the drug development process as possible and to avoid overexposing children to subtherapeutic doses. It is imperative that modeling and simulation approaches, together with identification and validation of additional PD end points, continue to evolve to enable development of the most effective therapies in the shortest amount of time. Additional research in both of these areas is warranted.

Declaration of Conflicting Interests

All authors are employees and shareholders of AbbVie Inc. Medical writing support was provided by Allison Kitten, an employee of AbbVie.

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