A Review of the Experience with Pediatric Written Requests Issued for Oncology Drug Products

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Abstract

Background Pediatric anticancer drug development has numerous challenges. Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA), has been put forth to address the deficiency in pediatric drug development in general. Until recently, the requirement for pediatric evaluation of most oncology products for adult cancers was waived, because children typically do not have adult-type cancers or the indication or drug had been granted orphan designation. PREA therefore had no impact. Pediatric studies for labeling updates are largely done through BPCA by a Written Request (WR), issued by FDA. Because pediatric and adult populations do not share the same biology, natural history, or disease progression, there are limited opportunities to extrapolate adult information to pediatric. The requirements for the pediatric studies can vary greatly. Procedure In this study, we searched WRs that were issued by the FDA since 2001. We found 42 requests for pediatrics in oncology drugs and biologics. Results Studies included in 25 of the WRs have concluded, 18 have been given exclusivity, and 4 drugs have been approved for use in pediatric populations. The current status of the WRs are presented from regulatory, study design, dosing, formulation, analysis plan, evidential standard of efficacy and safety. Conclusions This would serve the purposes to study what has been requested over the years and what have been completed in response to the requirements. We consider this to be the anchor of pediatric cancer development for current stage and can potentially provide insight on how pediatric cancer drug development would change for the future years.

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Abbreviations key:

WR	Written Requests
PREA	Pediatric Research Equity Act
BPCA	Best Pharmaceuticals for Children Act
PPSRs	Proposed Pediatric Study Requests
PK/PD	Pharmacokinetics / pharmacodynamics
DLT	Dose-limiting toxicity

Abstract:

Background

There are numerous challenges facing the field of pediatric oncology and hematology drug development. Two legislative initiatives, Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA), has been put forth to address the deficiency in pediatric drug development in general. Until recently, the requirement for pediatric evaluation of most oncology products for adult cancers was waived, because children typically do not have adult-type cancers (e.g. lung cancer) or because the indication or drug had been granted orphan designation. PREA therefore had no impact on pediatric anticancer drug development. Pediatric studies for labeling updates are largely done through BPCA by the fulfillment of a Written Request (WR), issued by the FDA. Because pediatric populations and adult populations do not share the same biology, natural history, or disease progression, there are limited opportunities to extrapolate adult information to pediatric. Therefore, the requirements for the pediatric studies can vary greatly according to the disease indications.

Procedure

In this study, we searched WRs that were issued by the FDA since 2001. We found 42 requests for pediatrics in oncology drugs and biologics.

Results

Of these WRs, studies included in 25 of the WRs have concluded, 18 have been given exclusivity, and 4 drugs have been approved for use in pediatric populations. We have presented the current status of the WRs from regulatory, study design, dosing, formulation, analysis plan, evidential standard of efficacy and safety.

Conclusions

This would serve the purposes to study what has been requested over the years and what have been completed in response to the requirements. We consider this to be the anchor of pediatric cancer development for current stage and can potentially provide insight on how pediatric cancer drug development would change for the future years.

Key words: pediatric, orphan indication, written request, cancer

Introduction

A 1968 editorial article in the Journal of Pediatrics referred to children as "therapeutic orphans" [1] to express the frustration of many clinicians over the lack of pediatric prescribing information for approved drugs [2]. For the past decades, pediatric cancer drug development has faced biological, societal and economic challenges, such as low prevalence patient population, concerns relating to ethical issues and perception of increased liability of testing drugs in children, companies not interested in pediatric studies and many more.

The Pediatric Research Equity Act (PREA) [3], which requires studies, and the Best Pharmaceuticals for Children Act (BPCA) [4], which provides the incentive of additional exclusivity for products of sponsors who conduct requested studies in the pediatric population, were enacted in 2003 and 2002 respectively, following the initial legislative provision for exclusivity in 1997 to correct this serious deficiency in drug development for young patients.

The requirement for pediatric evaluation of most oncology products developed for adult cancers is generally waived, because the common cancers which occur in adults and which are the focus of drug discovery and development efforts are never or very rarely seen in children or because the indication or drug had been granted orphan designation. PREA therefore has had no impact on pediatric anticancer drug development. Pediatric studies for labeling updates are largely done through BPCA by the fulfillment of a Written Request (WR), issued by the FDA. Because cancers in the pediatric and adult populations generally do not share the same biology, natural history and disease progression, full extrapolation from adults is unlikely, and requirements for the pediatric studies can vary greatly according to the disease indications. As a result, the requirements of oncology drug studies in WR can vary greatly.

The objective of this research is to identify, review, and evaluate all the written requests (WRs) for pediatric clinical trials regarding solid tumor and hematologic malignancies that were initially issued by the Food and Drug Administration between the dates January 1, 2001, and December 31, 2019. The authors from the Office of Biostatistics (OB), Office of Clinical Pharmacology (OCP) in CDER and Oncology Center of Excellence (OCE) have collaborated to review the content of WRs issued to sponsors for oncology drugs and biologics.

Methods

Selection of Studies

The information that has been summarized in this paper was gathered from the WRs that were issued by the FDA between the dates of January 1, 2001, and December 31, 2019 in response to Proposed Pediatric Study Requests (PPSRs). When the studies were completed and final clinical summary reports submitted in response to WRs, a comprehensive survey was conducted on the study results and corresponding FDA reviews, as well as published papers related to the pediatric studies. We excluded those pediatric WRs submitted to the National Institute of Child Health and Development, National Institutes of Health (NIH) for off patent drugs.

Technical Information

For each WR, key information included , but was not limited to specific pediatric cancer indications, feasibility of extrapolation from adults trials, number of studies requested, number of cohorts, types and phases of the studies (phase 1/2 dose-escalation/dose-finding, signal of activity seeking or phase 3), study drugs (monotherapy, combination), study designs (single-arm or with control, any blinding, dose levels and more), age range, study endpoints, number and reasons for amendments. For the studies submitted to fulfill WR, key information was captured, including patient accrual in the trials supporting WR, statistical methods used for efficacy evaluation, primary results, dose levels, starting dose selection, pharmacokinetics (PK) / pharmacodynamics (PD) sampling and analysis, unique dose-limiting toxicity (DLT) observed in children and special formulations developed for children. Finally, the current status of the WR was summarized, and whether or not pediatric exclusivity was granted.

A single written request generally contains more than one study and more than one cohort/indication since the statutory language requires that all possible pediatric indications for which the investigational drug

might provide clinical benefit be included in the assessment of the drug. Because labeling updates and regulatory actions are taken for individual drug, therefore, the results were summarized for each WR rather than individual studies in WR. The number of patients included in each WR was obtained by summing the numbers of study subjects among all studies and cohorts/indications included in the WR. If any one of the studies has a control/comparator arm, the WR is categorized as controlled. If any one of the studies in WR employed monotherapy, the WR is considered that the monotherapy activity was established.

In the study, the primary and secondary endpoints, were grouped into the following types: response rate endpoints, including overall response rate (ORR), complete response rate (CR), and complete remission (CR), which are binary; time to event (TTE) endpoints, including overall survival (OS), disease-free survival (DFS), Event-free survival (EFS) and progression-free survival (PFS); dose finding endpoints, including determination of maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D); PK/PD endpoints; safety endpoints; and any other endpoints, including change from baseline and unspecified or exploratory efficacy endpoints.

Completed WRs are those where complete study report from the WR studies were submitted to the FDA in the form of product supplement or labeling revision as a sNDA/BLA. The completed WRs were categorized as such if any of the following were met: exclusivity granted, denied exclusivity, under review, completed but fail to submit reports according to timeline required in the written requests, and completed but no remaining exclusivity. In contrast, WRs were considered as "not completed" if any of the following were met: terminated, listed as withdrawal/released, or categorized as ongoing.

Unique DLTs is defined as DLTs that are only found in pediatric patients. This excludes those observed in adult DLTs or adult adverse reactions.

Because children differ from adult including capacities for drug administration, medicine-related toxicity and taste preference, different formulation for children may be needed through requirement of special formulation development. This includes different formulations from marketed adult formulations, for example hazardous-substance-free ingredients for children, different administrative solutions (such as oral solution for small children that are unable to swallow tablets), and special developments (such as different shapes and colors to increase palatability.)

Results

Overall/Regulatory

During the 19-year, the Food and Drug Administration (FDA) issued 42 written requests to study drug products for solid tumors and/or hematologic malignancies in the pediatric population. Of these studies included in 42 WRs, 29 were on pediatric solid tumors, 18 were on pediatric hematologic malignancies, and 5 of these WRs covered both solid tumor and hematologic malignancies. The WRs that were identified include pediatric oncology trials conducted in pediatric patients from the neonatal period up to the age of 17. A few of the clinical trials included young adults up to the age of 30. The list of drugs issued in the WRs, the initial request dates, current status of each WR, the approved age range and languages related to WRs included in the labeling are shown in Table 1.

For the current status of the WRs, 15 out of 29 solid tumor WRs and 11 out of 18 hematologic malignancies WRs have completed (23 out of 42 WRs completed in total with 3 completed in both solid tumor and hematologic malignancies). Ninety-two percent (21/23) of the completed WRs submitted reports to the FDA in accordance with the timeline required in written requests. Four oncology drugs for the treatment of pediatric solid tumor or hematologic malignancies resulted in approval of the product for pediatric use added in the US prescribing information (USPI) specifically for pediatric age groups.

Of the completed WRs, 13 out of 16 solid tumor WRs and 5 out of 13 hematologic malignancy WRs have been granted 6-month exclusivity. One WR was denied exclusivity because of insufficient patients enrolled to assess the efficacy or for insufficient ability to inform a description of pharmacokinetic (PK) parameters. Two pediatric trials were terminated or released due to safety concerns (1 WRs) or enrollment difficulty

(1 WR). Two WRs were completed; however, the timeline to submit had passed. Finally, 2 drugs have no remaining patent life. Therefore, there is no exclusivity to add.

Requests for amendments to the WRs were submitted to the FDA in 50% (21 WRs) of the 42 and 19% (8 WRs) were amended more than twice. Majority of the reasons for amending a written request include a change in age distribution reflecting accrual expectations in practice, a cancelation of planned studies, an updated timeline, an increase or decrease in disease cohorts, and adjustment to the study endpoints (e.g. adding/removing a safety or efficacy endpoint, and replacing MTD with RP2D). Other less common reasons for submitting amendments include a change of dose levels, a change of therapy, a change of formulations, and a change of statistical evaluation method or criteria.

TABLE 1: Lists of Issued Written Requests (WRs) between Jan. 1, 2001 and Dec. 31, 2019

Under BPCA, WRs typically require studies to be conducted in more than one indication. FIGURE 1 shows the number of disease indication distributions for WRs on solid tumor and hematologic malignancies (1a and 1b). Numbers of disease cohorts in these WRs range from 1 to 6 disease cohorts.

FIGURE 1. The distribution of disease cohorts for WRs and the number of patients enrolled for completed pediatric trials. The upper left panel (1a) shows the number of disease cohorts on solid tumors, the upper right (1b) shows that on hematological malignancies. The x axis represents the number of disease cohorts, and the y axis shows the number of WRs. For number of patients enrolled, the bottom left panel (1c) shows the number of patients enrolled for trials on solid tumors, the bottom right panel (1d) shows that for trials on hematological malignancies. The x axis represents the number of patients, the y axis shows the drug names. White bars represent number of patients required in written requests, black bars represent number of patients that actually enrolled in clinical trials. The white bars for a few drugs are missing because patient accrual information in those written requests are not specified.

Among the pediatric trials initiated since 2001 in 42 WRs, extrapolation from adult trials was planned or used to support efficacy in pediatrics for 5 drugs, given similar underlying pathobiology and mechanism of action in pediatric patients and adults. These drugs are Dabrafenib (Tafinlar), Trametinib (Mekinist) for treatment of solid tumors; and Ruxolitinib, Midostaurin (Rydapt), Nilotinib (Tasigna) for treatment of hematologic malignancies (TABLE 2).

TABLE 2: Drugs and Conditions where the Study Design or Approval was based on Extrapolation from adult trials

Study Designs

The study designs in this section are summarized based on amended WRs rather than original WRs if the studies completed and submitted were conducted according to amended WRs. The studies in 24 out of 29 solid tumor WRs have combined phase 1 and 2 studies. The studies in 2 WRs only included phase 2 studies because the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) in pediatrics was already established from trials conducted previously. Studies in 3 WRs were designed to have a tentative phase 2 study based on results from the phase 1 study. For hematologic malignancy WRs, studies in 12 out of 18 WRs conducted combined phase 1 and 2 studies, studies in 2 WRs conducted only a phase 1 study, and studies in 4 WRs conducted a phase 2 study only.

For solid tumors, studies in 14 WRs have a control arm, with 3 used placebo with either best supportive care (BSC) or standard of care (SOC) and the rest 11 included active control arms. The other trials in 15 WRs are designed as single-arm. As a comparison, for hematologic malignancies, majority (15 out of 18) was single-arm design and only 3 have an active control.

As for treatment arm, studies in 25 WRs for solid tumor and 13 WRs for hematologic malignancies used monotherapy as the treatment arm; studies in 4 WRs in solid tumor and 5 WRs in hematologic malignancies used combination therapies.

Study Endpoints

For efficacy endpoints, studies in 30 WRs used a response rate, a binary endpoint, as the primary endpoint. This includes studies in 25 WRs used overall response rate (ORR) assessed by investigators, 2 used overall response rate assessed by independent review committees (IRC), 5 used a complete response (CR) rate assessed by investigators and 1 used a complete response rate assessed by an IRC. Some studies have both ORR and CR rates evaluations. Pediatric trials in 5 WRs used the time to event as efficacy endpoint, with 2 using event-free survival (EFS), 1 progression- free survival (PFS) assessed by investigators, and 2 used progression-free survival (PFS) assessed by an IRC.

Within one WR, typically a dose-escalation/dose-determination phase/study is required to evaluate the PK, safety, and preliminary activity of the drug to establish the MTD and/or RP2D in pediatric patients. For programs where the extrapolation from adult efficacy was feasible, the dose-finding phase/study was to identify the optimal safe and tolerable dose in pediatrics that achieves similar exposures to those achieved in adults. Other studies require different primary endpoints: 18 pediatric trials included PK/PD endpoints, 14 pediatric trials used safety related primary endpoint and 11 used other primary endpoints include clinical activity such as a change from baseline or other unspecified efficacy or activity endpoints.

Commonly used secondary endpoints include response rate, time to event endpoints, PK/PD endpoints, safety endpoints, and many other endpoints such as palatability and electrocardiogram measures.

Analysis and Sample Size

A minimum number of patients is typically required for individual study. We compared the number of patients required in the WR vs the number actually enrolled to fulfill the WR when the WR is completed. The result is plotted in FIGURE 1, 1c and 1d. Most pediatric trials recruited more patients than requested.

Safety Evaluation

Unique dose limiting toxicity (DLT) that are only found in pediatric patients was observed in several drug (TABLE 4).

Irinotecan HCl (Camptosar) has reported different adverse event profile in pediatric patients from adults in that dehydration associated with severe hypokalemia and hyponatremia. Nilotinib (Tasigna) reported to have observed growth retardation. Sunitinib malate (Sutent) has reported dose-limiting cardiotoxicity, which prompted amendment of the study to exclude patients with previous exposure to anthracyclines or cardiac radiation.

TABLE 3. Unique DLTs observed in oncology pediatric trials in response to written requests initiated since 2001.

Efficacy Evaluation

Efficacy endpoints used for supporting approvals in WRs include overall response rate (ORR), complete response(CR), event-free survival (EFS), and progression-free survival (PFS).

Efficacy evaluation methods that have been used are Cochran–Mantel–Haenszel test for response rate endpoints, Kaplan-Meier curve for time to event endpoints, t-test, and analysis of covariance (ANCOVA) for change from baseline endpoints.

Studies in nineteen WRs were designed to be powered to evaluate the primary efficacy. Among those 19 WRS, 12 WRs are considered completed. In the actual results submitted in response to WRs, only seven were able to conduct hypothesis testing in actual trials. Main reasons for not able to conduct hypothesis testing are due to present efficacy results descriptively.

PK/PD Evaluation

Pharmacokinetics and/or pharmacodynamics evaluation was required in all WRs and listed as primary endpoint in 18 pediatric studies. In all competed or ongoing studies in response to the WRs, PK samples were

collected through rich or sparse sampling to be analyzed with Population PK analysis and/or noncompartmental PK analysis. Key PK parameters (AUC, Cmax, Clearance, and volume of distribution, etc) were obtained. Depending on the planned age range for each study, PK collection was required from a minimum of 6-10 patients in each of the following age groups: 1 month to < 2 years or 12 months to < 6 years, 6 to < 12 years, and 12 to <18 years of age. Using combined data from available studies, Population PK/PD modeling and/or exposure-response analysis for safety and efficacy were conducted or planned to determine the optimal dose in the target pediatric population. In recent WRs for large molecules, characterization of immunogenicity was also required.

Starting dose Selection

The information for starting dose in phase 1 pediatrics studies was obtained for 37 WRs. The approaches for starting dose selection generally fall in two categories: empirical, and PK modeling and simulation. A summary of methods used for each approach by disease type is shown in Table 5. Majority of the program used the empirical approach of selecting a starting dose equivalent to 100% (most common for hematological malignancy) or ˜80% (most common for solid tumor) of body size adjusted adult dose, while 7 programs used 50-70% of adult MTD or RP2D to initial their phase 1 dosing-finding studies. As a comparison, PK modeling and simulation was used to identify the starting dose in pediatric patients for 7 drugs. This approach typically includes allometric scaling of adult PK parameters (ie, clearance and volume of distribution) based on body weight in children, and account for developmental factors such as organ and enzyme maturation where ontogeny functions are added for the dose projection. For one program, non-clinical data in murine model was also used to inform the starting dose selection for a combination therapy, along with data from ealier monotherapy study in pediatrics.

TABLE 4: Methods for starting dose selection in pediatric oncology studies in response to written requests initiated since 2001.

Formulation

Age-appropriate formulation is required for pediatric studies. Per the WR, the sponsors must develop and test an age-appropriate formulation if one is not currently available. Special formulations have been developed for several drugs in response to the WRs initiated since 2001, as shown in TABLE *6* .

TABLE 5: Special formulations developed in oncology pediatric trials in response to written requests initiated since 2001.

Discussion

Thoughtful drug development and inclusion of pediatric patients in trials is critical to public health. Over the years, because of rarity of pediatric cancer, pediatric cancer drug development has relied on BPCA rather than PREA to promote the development and inclusion of pediatric information into the drug label. Under FDA Reauthorization Act (FDARA) of 2017 and RACE for Children Act [25], pediatric studies for oncology products will no longer be exempt based on orphan designation, and the pediatric studies will be required for drugs directed at molecular targets observed in pediatric cancers [26]. Original marketing applications in the US for certain adult oncology drugs that are submitted on or after August 18, 2020 would be required to be preceded by plans for pediatric cancer investigations. With the change, pediatric oncology drug development should generally be coordinated with oncology drug development for adults, as part of an overall drug development plan.

Before the changes of FDARA and RACE Act take place, we conducted research on the written requests requested through BPCA over 19-year period. This would serve the purposes to study what has been requested over the years and what have been completed in response to the requirements. We consider this to be the anchor of pediatric cancer development for current stage and can potentially provide insight on how pediatric cancer drug development would change for the future years.

Since 2001, FDA has issued 42 written requests in the area of oncology. Among those, 18 drugs have

been granted additional pediatric exclusivity, and 4 received approval for use in specific age groups with indication in drug label. Most oncology pediatric trials have been designed to evaluate both safety and efficacy. The majority of pediatric trials in response to WRs included monotherapy activity evaluation. Request over the years has seen that more recent pediatric trials changed to request whether phase 2 studies should be conducted are based on results from the phase 1 study. Most pediatric trials are single arm design, especially for hematology indications. Although controlled trials are preferred, they are difficult to conduct in a pediatric population for ethical reasons. Most efficacy endpoints involved overall response rate and assessed by investigators. Only a few assessed the response rates by an independent review committee (IRC).

More pediatric studies are still in urgent need. Accrual challenge is the main reason for study termination. Many studies terminated because of difficulties with enrollment. On the other hand, many completed trials had the problem of over-accrual. Most of the completed pediatric trials over the past 19 years have led to conclusions that cancer drugs used in adult populations do not work as well in children. Since children are a vulnerable population, it is challenging to enroll them in clinical trials where the effects of these developmental drugs are unclear. Given the uncertainty in drug efficacy and for the protection of pediatric patients, the implementation of futility criteria into the trial design would be recommended in future pediatric trials. Studies should stop early if evidence of no efficacy is observed to minimize the harm to pediatric patients.

Because of many challenges in pediatric cancer drug development, innovative analysis should be explored to improve the efficiency of the pediatric trials. A Bayesian approach is a flexible tool that could be used in pediatric trials to sequentially monitor efficacy and futility as data accumulate [27]. This approach provides an option to stop trials for efficacy or futility if enough evidence is observed, and thus with the advantages of possibly requiring fewer patients and shorter trials. Bayesian approach in pediatric trials can formally incorporate prior information from adults, older age groups, and other external sources if appropriate and quantify the uncertainty. To overcome the limitation of a small population and limited opportunities for extrapolation, an innovative approach using Bayesian strategy to allow more flexibility in statistical design for future pediatric trials should be considered.

Identifying an optimal starting dose remains important for successful pediatric oncology drug development. Modeling and simulation is a powerful tool to inform selection of safe and efficacious doses as early as possible in the drug development process and to avoid overexposing children to subtherapeutic doses. When the disease pathobiology and the mechanism of action for drug would not differ by age, a starting dose may be selected by targeting similar exposure to the adult therapeutic dose without the need to evaluate multiple dose levels. When similarity in disease between pediatric and adults cannot be assumed, a more extensive PK and dose finding study may be required. While traditional designs like the 3+3 and rolling 6 are commonly used for dose escalation, Bayesian designs like the continual reassessment method or adaptive logistic regression design could be preferable, especially for targeted therapies with adult's safety profile well characterized.

We believe this research provides the sponsors, patient advocate groups, academic groups, and treating physicians on the current landscapes of pediatric studies in support of labeling changes and approved pediatric use of oncology and hematology drugs. Overall, this study will benefit the planning of future drug development in oncology and hematology in the pediatric population.

Conflict of Interest

The authors have no conflicts of interest to disclose. JY is currently an employee of BeiGene Ltd, and the work is completed while employed at FDA.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created in this study.

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