U.S. GOVERNMENT ACCOUNTABILITY OFFICE

441 G St. N.W.
Washington, DC 20548

January 31, 2023

Chair
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Cathy McMorris Rodgers
Chair
The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

Pediatric Cancer Studies: Early Results of the Research to Accelerate Cures and Equity for Children Act

Pediatric cancer is the leading cause of death by disease past infancy among children from birth to age 14 in the United States, according to the National Cancer Institute. The National Cancer Institute estimated that in 2022 alone, 10,470 new cases of cancer would be diagnosed in children—of those, around 10 percent are expected to ultimately die from the disease.[1] While survival rates for pediatric cancers more broadly have improved over the last few decades, survival rates for some pediatric cancers remain low. For example, the National Cancer Institute reports that only 10 percent of children with diffuse intrinsic pontine glioma, a rare brain tumor, survive 2 years after being diagnosed.

There have been relatively few drugs approved to treat pediatric cancer. As of December 2022, there were 54 drugs approved to treat pediatric cancer.[2] As a result, clinicians treating pediatric patients have limited options. Clinicians may opt to use a cancer drug approved for adults; however, in these instances, there may be limited available information specific to the safety and effectiveness of the drug in the pediatric population, according to Food and Drug Administration (FDA) officials.[3]

[1]National Cancer Institute, "Childhood Cancers" (Aug. 19, 2022), accessed Nov. 2, 2022, https://www.cancer.gov/types/childhood-cancers.

[2]Food and Drug Administration, "Pediatric Oncology Drug Approvals" (Dec. 2022), accessed Jan. 18, 2023, https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology-drug-approvals.

[3]Unapproved use of an FDA-approved drug is often called "off-label" use. Food and Drug Administration, "Understanding Unapproved Use of Approved Drugs 'Off Label'," (Feb. 5, 2018), accessed Dec. 6, 2022, https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label. FDA officials noted that much of the pediatric cancer standard of care management includes use of cancer drugs not specifically approved for use in children.

Pediatric Cancers
Pediatric oncologists often note that children are not just little adults. Children are less likely to suffer from some common adult cancers like lung, breast, colon, and prostate cancer.

Instead, the most common cancers among pediatric patients are brain and central nervous system cancers, leukemia (blood cancers), and Hodgkin and non-Hodgkin lymphomas (lymphatic cancers).

Brain and central nervous system cancers. The growth of abnormal cells in brain tissue and central nervous system.

Leukemia. Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

Lymphoma. Comprised of two basic categories—Hodgkin and non-Hodgkin lymphomas, these are cancers that begin in the cells of the immune system.

Source: GAO summary of information from the National Cancer Institute. I GAO-23-105947

Since 2003, to encourage research into pediatric treatments, sponsors of certain adult drugs and biologics (we refer to both as drugs in this report) have been required to conduct pediatric studies as part of the drug approval process per the Pediatric Research Equity Act of 2003.[4] However, this requirement has frequently been waived for sponsors of adult cancer drugs, because adults and children typically get different types of cancer.[5] For example, FDA would not have required a sponsor to conduct a pediatric study for a prostate cancer drug, because prostate cancer generally does not occur in children.

In more recent years, researchers have improved their understanding of cancers and are developing drugs that target the disease at the molecular level—referred to as molecularly targeted drugs.[6] With this approach, a drug that targets a molecular abnormality found in both adult and pediatric cancers can potentially be used to treat both populations, although their cancer types may differ.

Recognizing the potential of molecularly targeted drugs and to facilitate the development of new, safe, and effective drugs to treat children, Congress passed, and the President signed into law, the FDA Reauthorization Act of 2017, to include a provision commonly known as the Research to Accelerate Cures and Equity for Children Act (RACE Act).[7] Specifically, as of August 18, 2020, the RACE Act requires drug sponsors that intend to apply for approval of molecularly targeted adult cancer drugs to submit their planned approach for studying the drug in the pediatric population (referred to as an initial pediatric study plan).[8] The RACE Act requirement also applies to molecularly targeted adult cancer drugs that qualify as orphan drugs—generally, drugs intended to treat a disease or condition that affects fewer than 200,000 people in the U.S.

[4]The National Cancer Institute defines a biologic drug as a substance that is made from a living organism or its products, and is used in the prevention, diagnosis, or treatment of cancer and other diseases. A sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

[5]Under the Pediatric Research Equity Act of 2003, applications for new active ingredients, indications, dosage forms, dosing regimens, or routes of administration are generally required to include pediatric studies. FDA may grant a full or partial waiver of this requirement if certain conditions are met—for example, if the product is intended to treat a disease or condition that does not occur in a pediatric population. See 21 U.S.C. § 355c(a)(1)(A), (a)(2), and (a)(5). For our prior work on this act, see GAO, *Pediatric Research: Products Studied under Two Related Laws, but Improved Tracking Needed by FDA*, GAO-11-457 (Washington, D.C.: May 31, 2011).

[6]In this process, researchers first identify molecular targets associated with the cancer—for example, some proteins may be present in cancerous cells but not in non-cancerous cells. Then, researchers develop a drug that binds or interacts with the molecular target, thereby slowing or stopping the progression of cancer cell growth.

[7]Pub. L. No. 115-52, § 504, 131 Stat. 1005, 1039-46 (codified at 21 U.S.C. § 355c).

[8]RACE Act studies are generally required for original applications for new active ingredients if the drug is intended to treat an adult cancer and directed at a molecular target that is substantially relevant to the growth or progression of a pediatric cancer. FDA may grant a full or partial waiver of this requirement if certain conditions are met. See 21 U.S.C. § 355c(a)(1)(B), (a)(3), and (a)(5).

The FDA Reauthorization Act of 2017 includes a provision for GAO to review the effectiveness of the pediatric study requirements enacted by the RACE Act.[9] In this report, we describe the effects of the act.

To describe the effects of the RACE Act, we reviewed data provided by FDA officials on new molecularly targeted adult cancer drugs with initial pediatric study plans for the period from the implementation of the RACE Act requirement (August 18, 2020), through August 18, 2022. These data describe the 85 initial pediatric study plans that FDA received, reviewed, and agreed to during this time period.[10] We used these data to determine the number of pediatric cancer studies sponsors planned to conduct and the number expected to receive waivers, among other information. We assessed the reliability of these data by comparing them to information in other sources, such as FDA drug approval letters and an April 2022 FDA report to Congress; interviewing knowledgeable agency officials about the data; and performing checks of the data for accuracy and completeness.[11] Based on these steps, we found these data to be reliable for the purposes of our reporting objective.

Additionally, to learn more about the effects of the RACE Act, we conducted interviews with FDA officials and a judgmentally selected sample of 14 non-federal stakeholders. To capture a broad range of perspectives, including those of the drug industry and patients, we selected and interviewed individuals from four patient advocacy groups, two industry groups, and five drug sponsors, as well as three pediatric cancer researchers. The views of the 14 stakeholders are not generalizable; however, they provide insights on the effects of the RACE Act, including related benefits and challenges experienced since its implementation.

We conducted this performance audit from March 2022 through January 2023 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objective.

Background

FDA guidance encourages sponsors of adult molecularly targeted cancer drugs to meet with the agency early in the clinical study process to discuss their initial pediatric study plans.[12] The required components of an initial pediatric study plan include

[9]Pub. L. No. 115-52. § 504(f), 131 Stat. at 1045-46.

[10]FDA received and agreed upon at least two additional pediatric study plans prior to implementation of the RACE Act requirement. According to FDA officials, these plans were submitted by sponsors in anticipation of the RACE Act requirement.

[11]Food and Drug Administration, *Best Pharmaceuticals for Children Act and Pediatric Research Equity Act Status Report to Congress July 1, 2015–June 30, 2020* (Apr. 21, 2022).

[12]Sponsors are required to submit their initial pediatric study plan to FDA for review no later than 60 calendar days after the date of the end-of-phase 2 meeting, or at another time as agreed upon between FDA and the sponsor. The purpose of the end-of-phase 2 meetings is to determine the safety of proceeding to phase 3 clinical trials, to evaluate the phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

- an outline of the pediatric study or studies that the sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints—the result measured to determine effectiveness—and statistical approach);
- any request for a full waiver, partial waiver, or deferral along with supporting justification; and
- other information specified in the regulations issued by FDA.[13]

In some cases, a sponsor may believe that a pediatric study is not warranted or is not suitable for some pediatric age groups. These sponsors can use their initial pediatric study plan to request that FDA waive their pediatric study requirements entirely (referred to as a full waiver) or waive the pediatric study requirements for some age groups (referred to as a partial waiver). Sponsors with required pediatric studies may also request permission to submit the reports of studies after the adult drug is approved—these are referred to as deferrals. Deferred pediatric studies then become postmarketing requirements—studies that a sponsor completes after FDA has approved a product for marketing.[14]

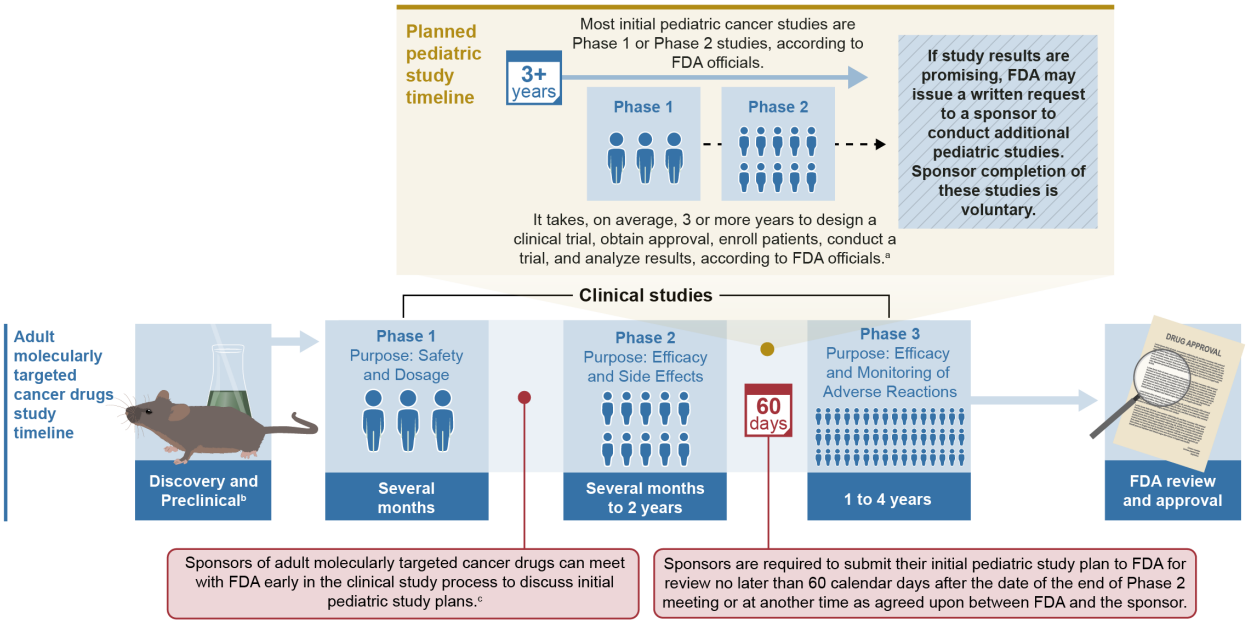
The required pediatric studies under the RACE Act are not necessarily designed to provide sufficient safety and effectiveness information for drug approval. RACE Act studies are designed to yield clinically meaningful pediatric study data about the drug's safety, dosing, and preliminary efficacy to inform potential pediatric uses of the drug. Depending on the results of a RACE Act study, FDA may choose to issue a written request to a sponsor to conduct additional pediatric studies, which may lead to eventual drug approval, if the drug is shown to be safe and effective in the pediatric population.[15] Sponsor completion of those additional study requests is voluntary. See figure 1 for an illustration of the drug development timeline and process with a pediatric study.

[13]See 21 U.S.C. § 355c(e)(2)(B). FDA guidance also notes that, in certain situations, it may be premature to include a detailed outline of a planned pediatric study (or studies) because additional data are needed. In these instances, the outline of the pediatric studies should include a brief explanation for the lack of more detailed information. Examples of other information that FDA recommends be included in such plans are a timeline for the pediatric development plan and agreements for pediatric studies with other regulatory agencies (for example, FDA's European counterpart, the European Medicines Agency) when available. Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans, Guidance for Industry* (July 2020).

[14]FDA reviews requests for a full waiver, partial waiver, or deferral in the initial pediatric study plan and makes a recommendation as to whether the request meets statutory criteria when it agrees to the plan. FDA does not finalize its decision on any request for a waiver or deferral until it approves the drug for use in adults.

[15]Before FDA can approve a drug, the sponsor must provide evidence to demonstrate the drug is safe and effective for its intended use. According to FDA officials, in some cases, a sponsor's initial pediatric study plan has included plans for more definitive studies that may be sufficient for approval for use in the pediatric population. Agency officials noted that decisions related to approval are made following sufficient FDA review of the application.

Figure 1: Illustrative Example of Drug Development Timeline and Process with a Pediatric Study



Source: GAO analysis of Food and Drug Administration (FDA) documentation and information provided by FDA officials. | GAO-23-105947

Note: This figure provides an illustrative example and is not intended to represent the path or time frames taken by all drugs and initial pediatric study plans. In this figure, GAO refers to both drugs and biologics as drugs.

[a]According to FDA officials, this timeline will vary based on several factors, including the rarity of the cancer, whether the pediatric study is international, and sponsor resources.

[b]In the discovery and development phase (referred to in the figure as "discovery"), researchers identify a promising drug compound for development through new insights and then conduct experiments to gather information on the compound. In the preclinical phase, researchers study a drug's toxicity in a laboratory setting so they can determine whether the drug has the potential to cause serious harm prior to testing in people.

[c]An initial pediatric study plan is a document that outlines the planned approach to study a drug in a pediatric population, which may include a plan to request a study deferral or waiver. While FDA makes a recommendation on any request for a waiver or deferral in an initial pediatric study plan, FDA does not finalize its decision until it approves the drug for use in adults.

The RACE Act Has Contributed to an Increase in Planned Pediatric Studies, but Long-Term Effects Are Unclear

The RACE Act Has Contributed to an Increase in the Number of Planned Pediatric Studies

The RACE Act has contributed to an increase in the number of pediatric studies that sponsors of molecularly targeted adult cancer drugs plan to conduct, according to data provided by FDA. Specifically, there have been 32 initial pediatric study plans submitted to FDA with intentions to conduct a pediatric study since the requirement was implemented on August 18, 2020, to August 18, 2022. Prior to the RACE Act, sponsors would not have been required to conduct most of these studies. This is either because (1) the drug has orphan status and would have been exempt from requirements to conduct a pediatric study or (2) the sponsor would have received a waiver, because the adult condition rarely or never occurs in children.[16]

[16]Under the Pediatric Research Equity Act of 2003, which predates the RACE Act, requirements for pediatric studies do not apply to orphan drugs. See 21 U.S.C. § 355c(k)(1). However, under the RACE Act, orphan drugs that are molecularly targeted cancer drugs are not exempt from pediatric study requirements. See 21 U.S.C. § 355c(k)(2). FDA has maintained a list of adult conditions that rarely or never occur in pediatric patients, and prior to the RACE Act, drugs intended for these conditions received a pediatric study waiver, as pediatric studies for these conditions would be impossible or highly impracticable. See 21 U.S.C. § 355c(a)(5).

Orphan Drugs
Orphan drugs include drugs for diseases affecting fewer than 200,000 people in the United States or for which there is no reasonable expectation of recovering the cost of the drug development and marketing from U.S. sales. Prior to the Research to Accelerate Cures and Equity for Children Act (RACE Act), all adult orphan drugs were exempt from pediatric study requirements—meaning that they did not have to study the drug in pediatric populations.

Postmarketing Requirements
Postmarketing requirements are studies that drug sponsors are required to conduct after FDA has approved a product for marketing. These studies provide additional information about the safety, efficacy, and optimal use of an approved drug.

Source: GAO summary of Food and Drug Administration (FDA) information. I GAO-23-105947

Specifically, of the 32 planned pediatric studies, five are for drugs that FDA has approved and have postmarketing requirements for pediatric studies, according to FDA documentation. Pediatric studies would not have been required for any of the five approved drugs prior to RACE Act implementation. (See enclosure I for more information on the adult and pediatric indications and molecular targets associated with these five approved drugs.) The remaining 27 planned pediatric studies are for drugs still in development—most of these planned studies would not have been required pre-RACE Act. See table 1 for more information on the planned pediatric studies that would have been exempt due to the drug's orphan status or received an adult indication waiver prior to the RACE Act.

Table 1: Planned Pediatric Studies under the RACE Act That Could Have Been Required Prior to RACE Act Implementation, August 18, 2020 through August 18, 2022

Drug approval status	Number of planned pediatric studies under RACE Act	Number of planned pediatric studies that would have received an exemption or waiver pre-RACE Act[a]	Number of planned pediatric studies that could have been required pre-RACE Act
Approved drugs	5	5[b]	0
Drugs in development	27	20[c]	7[d]
Total	**32**	**25**	**7**

Source: GAO analysis of data provided by Food and Drug Administration (FDA). | GAO-23-105947

Note: The RACE Act, or Research to Accelerate Cures and Equity for Children Act, is the common name for a provision included in the FDA Reauthorization Act of 2017

[a]Under the Pediatric Research Equity Act of 2003, which predates the RACE Act, requirements for pediatric studies do not apply to drugs for an indication for which orphan designation has been granted. See 21 U.S.C. § 355c(k)(1). These are commonly referred to as "orphan drugs." However, under the RACE Act, orphan drugs that are molecularly targeted cancer drugs are not exempt from pediatric study requirements. See 21 U.S.C. § 355c(k)(2). Orphan drugs are drugs that are intended to treat diseases affecting fewer than 200,000 people in the United States or for which there is no reasonable expectation of recovering the cost of the drug development and marketing from U.S. sales. FDA has also maintained a list of adult indications that rarely or never occur in the pediatric population, and prior to the RACE Act, drugs intended for these conditions received a pediatric study waiver, as pediatric studies for these indications would be impossible or highly impracticable. See 21 U.S.C. § 355c(a)(5).

[b]Four of the five approved drugs have orphan status, and the other approved drug is for a condition that rarely or never occurs in the pediatric population, and for which a pediatric study would be impossible or highly impracticable.

[c]Seventeen of the 27 drugs in development have orphan status, and three of the 27 drugs in development are for a condition that rarely or never occurs in the pediatric population, and for which a pediatric study would be impossible or highly impracticable.

[d]FDA officials noted that it was highly likely the agency would have waived requirements to conduct a pediatric study for the majority of the seven drugs noted in this column due to the rarity of the indication being sought in pediatric patients.

While the RACE Act has contributed to an increase in the number of planned pediatric studies, not all sponsors of molecularly targeted adult cancer drugs will be required to complete pediatric studies. Specifically, since RACE Act implementation, sponsors have submitted 53 other pediatric study plans to FDA for which FDA and the sponsor have agreed with the sponsor's plan to request a full waiver—meaning that a pediatric study would not have to be conducted.[17]

[17]While FDA makes a recommendation on any request for a waiver or deferral in an initial pediatric study plan, FDA does not finalize its decision until it approves the drug for use in adults.

Reasons for these waiver requests vary—for example, some sponsors requested waivers of the requirement because FDA and the sponsor determined the drug does not represent a meaningful therapeutic benefit over existing therapies for children and is not likely to be used in a substantial number of children. For more information on full waivers and the waiver justifications, as well as information on planned pediatric studies with partial waivers or deferrals, see enclosure II.

Long-Term Effects of RACE Act Are Not Yet Clear; FDA and Stakeholders Optimistic

It is too soon to know if the RACE Act will increase the number of drugs approved to treat pediatric cancers. This is because, according to FDA officials, the planned studies are still in the early phases or have not yet begun, so the final study outcomes, including whether they show promise in pediatric populations, are not yet known. These studies will take years to complete given the long timelines associated with pediatric drug development. For example, it will be at least 3 years before the first of the required pediatric studies for already approved adult drugs is completed and the associated reports are submitted to FDA, according to drug approval letters.

Additionally, because RACE Act studies are designed to yield clinically meaningful pediatric study data about the drug's safety, dosing, and preliminary efficacy to inform potential pediatric uses of the drug, FDA officials told us that additional studies may be needed for a drug to be approved for use in pediatric populations. These further studies are not required by the RACE Act. Instead, FDA may issue a written request to a sponsor to conduct additional pediatric studies.[18]

While the long-term effects of the RACE Act are not yet clear, FDA officials and nine stakeholders we interviewed including researchers, patient advocates, and drug sponsors told us they expect the RACE Act to have positive effects in furthering pediatric cancer research and drug development. For example, representatives from one drug sponsor we spoke with noted that since RACE Act implementation they have seen wider interest in pediatric cancer, which they view as a positive step. Officials with a research organization made similar comments, stating that they have received increased inquiries about conducting pediatric cancer studies. This positive outlook was echoed by FDA officials, who told us they are optimistic that the RACE Act will increase the number of drugs available for pediatric patients with cancer.

Patient Enrollment in Pediatric Studies Is Challenging; FDA Taking Steps to Address

Enrolling patients in pediatric cancer studies is a long-standing challenge due to limited patient populations. The increase in planned pediatric studies under the RACE Act could further exacerbate these enrollment challenges, according to FDA officials and six stakeholders we spoke with. Pediatric cancer, considered a rare disease, includes many subtypes of even more rare cancers. One researcher told us that the many different types and subtypes of pediatric cancers—each potentially needing its own study—can make potential patient population pools even narrower. Additionally, pediatric patients with cancer are often only enrolled in clinical studies when the existing cancer treatment fails or the patient has relapsed, further reducing the pool of potential enrollees, according FDA officials.

Because the patient population is so small, researchers may also face challenges finding study enrollees who are diverse and representative of the wider pediatric cancer population. According to recent research, pediatric cancer clinical studies may not always be representative

[18]Sponsor completion of additional studies requested by FDA through a written request is voluntary. As an incentive, if a sponsor opts to conduct the requested studies, it can gain an additional 6 months of marketing exclusivity once the requested studies are completed, based on the terms outlined in FDA's written request. See 21 U.S.C. § 355a.

of a diverse population.[19] In April 2022, FDA published draft guidance that noted the importance of adequate representation of children from racial and ethnic minority backgrounds in pediatric clinical studies.[20]

Enrollment challenges have the potential to affect whether pediatric cancer studies are completed, and whether the data are sufficient to determine significant effects of the studied drug. Two researchers we spoke with expressed concerns that enrollment challenges could ultimately lead to pediatric studies not being completed.

FDA officials noted that they are prepared to work with sponsors to address enrollment challenges. FDA has taken steps intended to help address such challenges, including

- providing guidance on innovative study designs;
- coordinating with its European counterpart, the European Medicines Agency; and
- developing guidance on determining pediatric studies for similar drugs.

Providing guidance on innovative study designs. FDA's guidance for industry describes six innovative approaches sponsors may take to address small pediatric populations. For example, sponsors may be able to enroll pediatric patients in a cohort for an existing adult study, leveraging the resources of the adult study instead of opening up an entirely new clinical trial solely for pediatric patients.[21] FDA officials noted that several sponsors have included innovative study designs in their pediatric study plans. For example, FDA officials told us that there are initial pediatric study plans where the sponsor will study a drug or drug combination across multiple cancer populations, referred to as a basket trial. Basket trials minimize the number of patients needed for a clinical trial with a specific type of cancer, because researchers can draw from patient populations with multiple cancer types. A sponsor and an advocacy group we spoke with also noted the value of innovative study designs in overcoming enrollment challenges.

Coordinating with the European Medicines Agency. FDA guidance notes that coordination with its European counterpart—the European Medicines Agency, which has pediatric cancer study requirements that predate the RACE Act—can help prevent duplication of studies and competition for scarce pediatric patients with cancer. According to FDA officials, since RACE Act implementation, FDA and the European Medicines Agency have been working closely, including holding joint discussions regarding the scientific and clinical justification for pediatric studies of new adult cancer drugs, their feasibility given the limited patient populations, the appropriate timing of studies, and study designs and timelines.[22] The value of this coordination

[19]Paula Aristizabal et al., "Disparities in Pediatric Oncology: The 21st Century Opportunity to Improve Outcomes for Children and Adolescents with Cancer," *American Society of Clinical Oncology Educational Book*, vol. 41 (2021).

[20]Food and Drug Administration, *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Draft Guidance for Industry*, (Apr. 2022).

GAO has also examined diversity in cancer clinical trials more broadly, see GAO, *Cancer Clinical Trials: Federal Actions and Selected Non-Federal Practices to Facilitate Diversity of Patients*, GAO-23-105245 (Washington, D.C.: Dec. 22, 2022).

[21]Food and Drug Administration, *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act. Guidance for Industry* (May 2021).

[22]According to FDA guidance for industry, the European Medicines Agency and FDA work together to provide common commentary on some proposed pediatric study plans and also have a mechanism for formal parallel

was echoed by drug sponsors. For example, two sponsors said cooperation between FDA and the European Medicines Agency was important and could potentially allow sponsors to fulfill both agencies' pediatric study requirements with a single study.

Developing guidance on determining pediatric studies for similar drugs. FDA officials told us that the agency is developing guidance for determining pediatric study requirements among multiple same-in-class drugs. These drugs have the same molecular target and are in the same pharmacologic class, meaning they function similarly to each other. Because pediatric studies of same-in-class drugs will draw from the same small patient pool, there are concerns that sponsors may struggle to enroll enough patients, according to FDA officials and four stakeholders we spoke with, including one researcher, one industry association, and two drug sponsors. Three sponsors and an industry association we spoke with noted that it is helpful in drug development planning to understand how FDA makes decisions regarding which same-in-class drugs require a pediatric study, and which will have their requirements waived. FDA officials told us the guidance will likely take a few years to develop and finalize, including time for public comment.[23]

Agency Comments

We provided a draft of this report to the Department of Health and Human Services (HHS) for review and comment. HHS provided technical comments, which we incorporated as appropriate. We are sending copies of this report to the appropriate congressional committees and the Secretary of Health and Human Services. In addition, the report will be available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or DeniganMacauleyM@gao.gov. Contact points for our offices of Congressional Relations and Public Affairs may be found on the last page of this report. In addition to the contact named above, Deirdre Brown (Assistant Director), Luke Baron (Analyst-in-Charge), Maggie Baucom, and Meghann Lewis made key contributions to this report. Also contributing were Joycelyn Cudjoe, Kaitlin Farquharson, Ying Hu, Roxanna Sun, and Janet Wilson.

Mary Denigan-Macauley
Director, Health Care

Enclosure(s) – 2

scientific advice from both agencies for some cancer drug applications. Food and Drug Administration, *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs.*

[23]In May 2022, FDA held a public meeting with its Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee to discuss the RACE Act, including challenges with same-in-class drugs.

Enclosure I: List of Molecular Targets and Associated Adult and Pediatric Indications in Planned Pediatric Studies

The FDA Reauthorization Act of 2017 includes a provision commonly known as the Research to Accelerate Cures and Equity for Children Act (RACE Act). The RACE Act requires sponsors of certain adult drugs that target cancer at the molecular level—referred to as molecularly targeted drugs—to submit plans to study the drug in the pediatric population (referred to as an initial pediatric study plan) to the Food and Drug Administration (FDA).[24] Included in these plans are the adult cancer that the adult drug is intended to treat, the associated molecular target—for example a protein present in a cancerous cell that is not present in a non-cancerous cell—and (when available) the pediatric cancer the sponsor plans to study. Table 2 provides this information for the five FDA-approved molecularly targeted adult cancer drugs since the implementation of the RACE Act (August 18, 2020) through August 18, 2022 with planned pediatric studies.

Table 2: Cancer Types and Associated Molecular Targets for Approved Adult Cancer Drugs, August 18, 2020 through August 18, 2022

Pediatric cancer	Adult cancer	Molecular target[a]
Relapsed/refractory B-cell non-Hodgkin lymphoma	Relapsed/refractory diffuse large B-cell lymphoma	CD19
Recurrent/refractory low-grade glioma, other advanced solid tumors	Cholangiocarcinoma	FGFR
Relapsed/refractory tissue factor expressing tumors	Cervical cancer	F3 (Tissue Factor)
Melanoma	Melanoma	LAG3
Philadelphia chromosome positive chronic myeloid leukemia in chronic phase	Philadelphia chromosome positive chronic myeloid leukemia chronic phase	ABL1, ABL2

Source: GAO analysis of data provided by the Food and Drug Administration. | GAO-23-105947

[a]A molecular target is a molecule involved in the growth or spread of cancer cells. A molecularly targeted drug binds or interacts with the molecular target, thereby slowing or stopping the progression of cancer cell growth. For example, a drug may interact with a protein that is present in a cancerous cell but not present in a non-cancerous cell.

[24]Pub. L. No. 115-52, § 504, 131 Stat. 1005, 1039-46 (codified in relevant part at 21 U.S.C. § 355c(e)).

A sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. For the purposes of this report, we refer to both drugs and biologics as drugs.

A molecularly targeted drug binds or interacts with the molecular target, thereby slowing or stopping the progression of cancer cell growth. For example, a drug may interact with a protein that is present in a cancerous cell but not present in a non-cancerous cell.

Enclosure II: Pediatric Study Requirement Waiver, Partial Waiver, and Deferral Justifications

The FDA Reauthorization Act of 2017 includes a provision commonly known as the Research to Accelerate Cures and Equity for Children Act (RACE Act). The RACE Act requires sponsors of certain adult drugs that target cancer at the molecular level—referred to as molecularly targeted drugs—to submit plans to study the drug in the pediatric population (referred to as an initial pediatric study plan) to the Food and Drug Administration (FDA) for review and agreement.[25] Sponsors are required to submit their initial pediatric study plan to FDA for review no later than 60 calendar days after the date of the end-of-phase 2 meeting, or at another time as agreed upon between FDA and the sponsor.[26]

In their initial pediatric study plans, sponsors may include a plan to request a full waiver, partial waiver, or deferral of pediatric study requirements.

- A full waiver means the sponsor does not need to conduct a pediatric study.
- A partial waiver allows the sponsor to exclude certain pediatric populations from the pediatric study. For example, if a drug is intended for patients who have failed existing treatment options, a sponsor may justify a planned request for a partial waiver for children under 1 year of age because they are unlikely to have exhausted available treatment options.
- A deferral allows sponsors with required pediatric studies to submit the study reports after the drug is approved for use in adults. Partial waivers and deferrals are not mutually exclusive—sponsors may receive a partial waiver and a deferral, allowing them to submit the reports for the pediatric study after the drug is approved for use in adults.[27]

Since the RACE Act was implemented on August 18, 2020 through August 18, 2022, there have been 53 initial pediatric study plans submitted to FDA for which FDA and the sponsor have agreed with the sponsor's plan to request a full waiver—meaning that a pediatric study would not have to be conducted.[28] See table 3 for the justifications for these full waivers.

---

[25]Pub. L. No. 115-52, § 504, 131 Stat. 1005, 1039-46 (codified in relevant part at 21 U.S.C. § 355c(e)).

A sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. For the purposes of this report, we refer to both drugs and biologics as drugs.

A molecularly targeted drug binds or interacts with the molecular target, thereby slowing or stopping the progression of cancer cell growth. For example, a drug may interact with a protein that is present in a cancerous cell but not present in a non-cancerous cell.

[26]The purpose of the end-of-phase 2 meetings is to determine the safety of proceeding to phase 3 clinical trials, to evaluate the phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

[27]FDA reviews requests for full waivers, partial waivers, and deferrals in the initial pediatric study plan and makes a recommendation as to whether the requests meet statutory criteria when it agrees to the plan. FDA does not finalize its decision on any request for a waiver or deferral until it approves the drug for use in adults.

[28]According to data provided by FDA, of the 53 initial pediatric study plans for which FDA and the sponsor ultimately agreed with the sponsor's plan to request a full waiver, two did not initially include such a request. One sponsor initially requested a partial waiver but ultimately requested a full waiver, because the drug was a later generation

Table 3: Number of Initial Pediatric Study Plans with Plans to Request Full Waivers, and Associated Justifications, August 18, 2020 through August 18, 2022

Waiver justification	Number of initial pediatric study plans
Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients[a]	23
Evidence strongly suggests that the drug would be ineffective or unsafe in all pediatric age groups	1
Necessary studies are impossible or highly impracticable because, for example, the number of patients is so small or the patients are geographically dispersed	29
Total	**53**

Source: GAO analysis of data provided by the Food and Drug Administration (FDA). | GAO-23-105947

Note: An initial pediatric study plan is a document that outlines the planned approach to study a drug in a pediatric population, which may include a plan to request a full waiver. A full waiver means the sponsor does not need to conduct a pediatric study. FDA reviews requests for full waivers in the initial pediatric study plan and makes a recommendation as to whether the request meets statutory criteria when it agrees to the plan. FDA does not finalize its decision on any request for a waiver until it approves the drug for use in adults.

[a]This category may also include some same-in-class drugs. According to FDA officials, same-in-class drugs are drugs that have the same molecular target and are in the same pharmacologic class, meaning they function similarly to each other.

During this same time period, sponsors have submitted 32 initial pediatric study plans to FDA for which FDA and the sponsor have agreed that a pediatric study will be conducted. However, 25 of these 32 include plans to request a partial waiver.[29] (See table 4.)

Table 4: Number of Initial Pediatric Study Plans with and without Plans to Request Partial Waivers and Associated Justifications, August 18, 2020 through August 18, 2022

Waiver type	Waiver justification	Number of initial pediatric study plans
Partial waiver	Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in a specific pediatric age group and is not likely to be used by a substantial number of pediatric patients in that age group.	1
	Necessary studies are impossible or highly impracticable in a specific pediatric age group, such as infants.	21
	There is evidence strongly suggesting that the drug would be ineffective or unsafe in a specific pediatric age group.	3
Subtotal (partial waiver)		**25**
No waiver	Not applicable	7

product. Another sponsor initially requested a deferral but ultimately requested a full waiver, as the drug was deemed likely not to provide a meaningful therapeutic benefit over existing therapies for pediatric patients.

[29]According to data provided by FDA, of the 32 initial pediatric study plans, four of them originally included plans to request a full waiver. In these instances, FDA and the sponsor ultimately agreed that the sponsor would request a partial waiver (three drugs) or no waiver (one drug).

Total (partial waiver and no wavier)	**32**

Source: GAO analysis of data provided by the Food and Drug Administration (FDA). | GAO-23-105947

Note: An initial pediatric study plan is a document that outlines the planned approach to study a drug in a pediatric population, which may include a plan to request a partial waiver. A partial waiver means that the sponsor is not required to conduct a pediatric study for some pediatric patients. For example, a partial waiver may result in a sponsor not studying the drug in pediatric patients under the age of one. FDA reviews requests for partial waivers in the initial pediatric study plan and makes a recommendation as to whether the request meets statutory criteria when it agrees to the plan. FDA does not finalize its decision on any request for a waiver until it approves the drug for use in adults.

Further, of the 32 initial pediatric study plans, 30 include plans to request a deferral.[30] (Some sponsors may request a partial waiver and a deferral.) See table 5 for the justification of these deferrals.

Table 5: Number of Initial Pediatric Study Plans with Plans to Request Deferrals and Associated Justifications, August 18, 2020 through August 18, 2022

Deferral justification	Number of initial pediatric study plans
Pediatric studies should be delayed until additional safety or effectiveness data have been collected	14
Drug is ready for approval for use in adults before the pediatric study is completed	16
Total	**30**

Source: GAO analysis of data provided by the Food and Drug Administration (FDA). | GAO-23-105947

Note: An initial pediatric study plan is a document that outlines the planned approach to study a drug in a pediatric population, which may include a plan to request a deferral. A deferral allows sponsors with planned pediatric studies to submit the study reports after the drug is approved for adults. FDA reviews requests for deferrals in the initial pediatric study plan and makes a recommendation as to whether the request meets statutory criteria when it agrees to the plan. FDA does not finalize its decision on any request for a deferral until it approves the drug for use in adults.

(105947)

[30]According to data provided by FDA, 27 sponsors initially requested deferrals in their pediatric study plans. Of those 27, FDA agreed with 26 sponsors' plans to request a deferral. In one instance, FDA and the sponsor ultimately agreed that the sponsor would request a full waiver. Additionally, there were four sponsors that initially requested full waivers, but ultimately agreed with FDA to request deferred studies—three sponsors ultimately requested planned partial waivers and deferrals, and one ultimately requested a planned deferral.