
Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)**

**March 2019
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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	CRITERIA FOR INCLUDING ADOLESCENT PATIENTS IN ADULT ONCOLOGY CLINICAL TRIALS.....	2
IV.	DOSE SELECTION FOR ADOLESCENT PATIENTS IN ADULT ONCOLOGY CLINICAL TRIALS.....	3
V.	SAFETY MONITORING	4
VI.	ETHICAL CONSIDERATIONS.....	4

Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide the pharmaceutical industry, clinical investigators, and institutional review boards with information to facilitate the inclusion of adolescent patients (for purposes of this guidance, defined as ages 12 to 17) in relevant adult oncology clinical trials. FDA recommends the inclusion of adolescent patients in disease- and target-appropriate adult oncology clinical trials to enable earlier access to investigational and approved drugs² for adolescent patients with cancer. Topics that are discussed in this guidance include the following:

- Appropriate criteria for the inclusion of adolescent patients in adult oncology clinical trials at various stages of drug development
- Dosing and pharmacokinetic and pharmacodynamic evaluations
- Safety monitoring
- Ethical considerations

The information in this guidance is meant to serve as a general guideline for sponsors considering this approach. Because specific details of an adult oncology drug development program that includes adolescent patients will vary depending on the characteristics and development stage of the drug and disease(s) under evaluation, sponsors are encouraged to

¹ This guidance has been prepared by the Divisions of Hematology and Oncology Products and Clinical Pharmacology V in the Center for Drug Evaluation and Research and the Oncology Center of Excellence (OCE) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² For purposes of this guidance, references to *drugs* includes drugs and biological products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262) that are drugs.

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contact the responsible FDA review division to discuss details of the program before implementation.

In addition, enrolling adolescent patients in adult oncology clinical trials may contribute toward addressing pediatric regulatory requirements under section 505A or 505B of the Federal Food, Drug, and Cosmetic Act. Details of these requirements should be discussed with the responsible FDA review division.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Cancers in young pediatric patients are often different from those in adult patients and require unique treatment approaches; however, some cancers found in adolescent patients—such as some soft tissue and bone sarcomas, central nervous system tumors, leukemias and lymphomas, and melanoma—are similar in histology and biologic behavior to those found in adults. Adolescent patients, because of their age, have historically been ineligible for enrollment in adult oncology clinical trials, and the initial pediatric trials for many drugs are conducted years later, often after the drug is approved in adults. As a result, adolescent patients may have delayed access to potentially effective therapies. In addition, accrual of adolescent patients to pediatric trials evaluating approved drugs may be difficult because patients can receive the drug through off-label use.

III. CRITERIA FOR INCLUDING ADOLESCENT PATIENTS IN ADULT ONCOLOGY CLINICAL TRIALS

Adolescent patients should be eligible for enrollment in adult oncology clinical trials at all stages of drug development when the histology and biologic behavior of the cancer under investigation is the same in, or the molecular target of the drug is relevant to, cancers in both adult and adolescent patients.

The following are recommendations regarding including adolescent patients by stage of drug development:

- First-in-human or dose-escalation trials:
 - Adolescent patients may be enrolled after some initial adult pharmacokinetic and toxicity data are obtained. The sponsor should consult with the responsible FDA review division to determine the amount and type of adult data needed before enrolling adolescent patients.

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- In general, adolescent patients enrolled in these early phase trials should have cancers that are relapsed after or refractory to standard therapy with no curative options or for which no standard therapies with curative intent exist.
- Activity-estimating or confirmatory trials:
 - Adolescent patients can be enrolled simultaneously with adults

IV. DOSE SELECTION FOR ADOLESCENT PATIENTS IN ADULT ONCOLOGY CLINICAL TRIALS

Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after accounting for the effect of body size on pharmacokinetics. Selection of an appropriate dose for adolescent patients in clinical trials should be based on pharmacokinetic and/or pharmacodynamic characteristics of the investigational drug with consideration of body size effect on drug exposure, toxicity, and activity data (if available); the therapeutic index of the drug; and dose- and exposure-response relationships in adults.³

The following are recommendations for dosing based on how the drug is dosed in adults:

- For drugs with **body size-adjusted dosing** for adults, adolescent patients should receive the same body size-adjusted dose (mg/kg or mg/m²) that is administered in adults.
- For drugs administered as a **fixed dose** based on data showing no clinically meaningful body size effect on drug exposure and toxicity in adults, a minimum body weight threshold should be defined to prevent adolescent patients who have a lower body weight than average from exceeding adult exposures.
 - An FDA analysis of adult population pharmacokinetics of oncology drugs suggested that 40 kg (the approximate median body weight of a 12-year-old⁴) is generally the lower end of the body weight range that has no clinically relevant effect on drug pharmacokinetics or safety. (This cutoff may change based on the characteristics of the drug, including the effect of body size on pharmacokinetics, the therapeutic index, and dose- and exposure-response relationships.)
 - In general, adolescent patients who weigh at least 40 kg can receive the same fixed dose administered in adults.

³ Selection of an appropriate dose for adolescent patients may be more complex for certain biological products that are regulated by CBER. Sponsors of such products should consult with the relevant review division in CBER to determine if there are specific considerations they should take into account with respect to their products.

⁴ See the Clinical Growth Charts web page under National Center for Health Statistics at the Centers for Disease Control and Prevention website (https://www.cdc.gov/growthcharts/clinical_charts.htm).

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- In general, adolescent patients who weigh less than 40 kg should switch to a body weight (mg/kg) or body surface area (mg/m²) adjusted dose. This adjusted dose should be based on an adult reference body size (e.g., the average adult body weight of 70 kg or median body weight or surface area of the adult patient population determined from existing data).
- Pharmacokinetic and/or pharmacodynamic (if available) samples should be collected from adolescent patients included in the adult oncology drug development program.

V. SAFETY MONITORING

Safety data collected during the trial should be examined for any age-related differences.

The evaluation of developmental toxicities (e.g., growth derangements, fertility issues) that require a long duration of follow-up may not be possible in the context of early phase trials; however, the sponsor should develop a plan for longitudinal evaluation of potential developmental toxicities when it is feasible, particularly in trials enrolling patients in earlier lines of therapy.

Adolescent patients enrolled in adult oncology clinical trials should have access to appropriate care providers and facilities necessary to address the clinical management of potentially unique toxicities in this patient population, which may require pediatric oncology expertise.

Juvenile animal studies are not routinely needed before the enrollment of adolescent patients in adult oncology clinical trials, unless clinical and/or nonclinical data do not provide sufficient information on toxicities.⁵

VI. ETHICAL CONSIDERATIONS

Under 21 CFR 50.50, institutional review boards reviewing adult oncology clinical trials that allow for the enrollment of adolescent patients must ensure that the provisions of 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations, and, specifically, 21 CFR 50.52, Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects, are satisfied before approving the studies. Considerations should include disease and/or molecular target, available therapeutic options, and dose level for first-in-human trials.

Enrollment of appropriately selected adolescent patients in relevant adult oncology clinical trials with appropriate dose considerations and adequate safety monitoring is justified given the severe and life-threatening nature of their disease.

⁵ Leighton, JK, Saber H, Reaman G, and Pazdur R, 2016, An FDA Oncology View of Juvenile Animal Studies in Support of Initial Pediatric Trials for Anticancer Drugs, *Regul Toxicol Pharmacol*, Aug; 79:142–143.