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

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Meredith K. Chuk at 301-796-2320 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 (IRBs) 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 adolescents in disease- and target-appropriate adult oncology trials to enable earlier access to investigational and approved drugs[2] for adolescent patients with cancer. Considerations that are discussed in this guidance include:

- Appropriate criteria for the inclusion of adolescent patients in adult oncology trials at various stages of drug development
- Dosing and pharmacokinetic (PK) evaluations
- Safety monitoring
- Ethical requirements

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 adolescents will vary depending on the characteristics and development

[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 in cooperation with the Center for Biologics Evaluation and Research 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.

stage of the drug and disease(s) under evaluation, sponsors are encouraged to contact the responsible FDA review division to discuss details of the program before implementation.

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 adolescents, 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. Adolescents, because of their age, generally are not eligible for enrollment in adult oncology trials, and the initial pediatric trials for many drugs are conducted years later, often after the drug is approved in adults. As a result, adolescents may have delayed access to potentially effective therapies. In addition, accrual of adolescents to pediatric trials evaluating approved drugs may be difficult because of off-label use.

III. CRITERIA FOR INCLUDING ADOLESCENTS

Adolescents 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 when including adolescents by stage of drug development:

- **First-in-human or dose-escalation trials:**
  - Adolescents may be enrolled after initial adult PK and toxicity data are obtained. Sponsors should consult with the responsible FDA review division to determine the amount and type of adult data needed before enrolling adolescent patients.
    - If adolescents are to be enrolled in early dose cohorts, sponsors should ensure that the dose to be administered satisfies 21 CFR 50.52 (see section VI., Ethical Considerations).
  - In general, adolescents 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:**

  – Adolescents can be enrolled simultaneously with adults

IV. DOSING RECOMMENDATIONS

Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after taking into account the effect of body size on pharmacokinetics.

The following are general dosing recommendations:

- Selection of an appropriate dose for adolescents should be based on whether the adult dose is adjusted based on body size (weight or surface area) or is a fixed dose (i.e., not adjusted for body weight or surface area).

- The recommended dosing approach should be supported by the PK characteristics of the investigational drug with consideration of the effect of body size on its pharmacokinetics, the therapeutic index of the drug, and dose- and exposure-response relationships.

- PK samples in adolescents should be collected at the time adolescents are included in the drug development program and analyzed to verify similar drug systemic exposure in adolescents and adults.

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

- For drugs with **body size-adjusted dosing** for adults, adolescents should receive the same body size-adjusted dose (mg/kg or mg/m^2) that is administered in adults.

- For drugs administered as a **fixed dose** in adults, a minimum body weight threshold should be defined to prevent adolescents 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 average body weight of a 12-year-old[3]) 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, adolescents with body weight of at least 40 kg can receive the same fixed dose administered in adults.

[3] 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).

- In general, adolescents with body weight of less than 40 kg should switch to a body weight (mg/kg) or body surface area (mg/m^2) 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).

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, sponsors 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.

Juvenile animal studies are not routinely needed before the enrollment of adolescents in oncology clinical trials, unless clinical and/or nonclinical data do not provide sufficient information on toxicities.[4]

VI. ETHICAL CONSIDERATIONS

Under 21 CFR 50.50, IRBs reviewing adult oncology clinical trials that allow for the enrollment of adolescents 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.

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

[4] 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.