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# 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## *DRAFT GUIDANCE*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.

**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)**

**June 2018  
Clinical/Medical**

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# Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry<sup>1</sup>

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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<sup>2</sup> 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

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<sup>1</sup> 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.

<sup>2</sup> 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.

## ***Contains Nonbinding Recommendations***

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

40  
41 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
42 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
43 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
44 the word *should* in Agency guidances means that something is suggested or recommended, but  
45 not required.

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### **II. BACKGROUND**

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50 Cancers in young pediatric patients are often different from those in adult patients and require  
51 unique treatment approaches; however, some cancers found in adolescents, such as some soft  
52 tissue and bone sarcomas, central nervous system tumors, leukemias and lymphomas, and  
53 melanoma are similar in histology and biologic behavior to those found in adults. Adolescents,  
54 because of their age, generally are not eligible for enrollment in adult oncology trials, and the  
55 initial pediatric trials for many drugs are conducted years later, often after the drug is approved  
56 in adults. As a result, adolescents may have delayed access to potentially effective therapies. In  
57 addition, accrual of adolescents to pediatric trials evaluating approved drugs may be difficult  
58 because of off-label use.

59  
60

### **III. CRITERIA FOR INCLUDING ADOLESCENTS**

61  
62

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

67

68 The following are recommendations when including adolescents by stage of drug development:

69

#### **• First-in-human or dose-escalation trials:**

70  
71

- 72 – Adolescents may be enrolled after initial adult PK and toxicity data are obtained.  
73 Sponsors should consult with the responsible FDA review division to determine the  
74 amount and type of adult data needed before enrolling adolescent patients.  
75
- 76     ▪ If adolescents are to be enrolled in early dose cohorts, sponsors should ensure that  
77 the dose to be administered satisfies 21 CFR 50.52 (see section VI., Ethical  
78 Considerations).
- 79
- 80 – In general, adolescents enrolled in these early phase trials should have cancers that  
81 are relapsed after or refractory to standard therapy with no curative options or for  
82 which no standard therapies with curative intent exist.

83

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- 84       • **Activity estimating or confirmatory trials:**  
85  
86       – Adolescents can be enrolled simultaneously with adults  
87

#### 88 89 **IV. DOSING RECOMMENDATIONS**

90  
91 Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients  
92 after taking into account the effect of body size on pharmacokinetics.  
93

94 The following are general dosing recommendations:  
95

- 96       • Selection of an appropriate dose for adolescents should be based on whether the adult  
97 dose is adjusted based on body size (weight or surface area) or is a fixed dose (i.e., not  
98 adjusted for body weight or surface area).  
99
- 100       • The recommended dosing approach should be supported by the PK characteristics of the  
101 investigational drug with consideration of the effect of body size on its pharmacokinetics,  
102 the therapeutic index of the drug, and dose- and exposure-response relationships.  
103
- 104       • PK samples in adolescents should be collected at the time adolescents are included in the  
105 drug development program and analyzed to verify similar drug systemic exposure in  
106 adolescents and adults.  
107

108 The following are recommendations for dosing based on how the drug is dosed in adults:  
109

- 110       • For drugs with **body size-adjusted dosing** for adults, adolescents should receive the  
111 same body size-adjusted dose (mg/kg or mg/m<sup>2</sup>) that is administered in adults.  
112
- 113       • For drugs administered as a **fixed dose** in adults, a minimum body weight threshold  
114 should be defined to prevent adolescents who have a lower body weight than average  
115 from exceeding adult exposures.  
116
- 117       – An FDA analysis of adult population pharmacokinetics of oncology drugs suggested  
118 that 40 kg (the average body weight of a 12-year-old<sup>3</sup>) is generally the lower end of  
119 the body weight range that has no clinically relevant effect on drug pharmacokinetics  
120 or safety. (This cutoff may change based on the characteristics of the drug, including  
121 the effect of body size on pharmacokinetics, the therapeutic index, and dose- and  
122 exposure-response relationships.)  
123
- 124       – In general, adolescents with body weight of at least 40 kg can receive the same fixed  
125 dose administered in adults.  
126

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<sup>3</sup> 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](https://www.cdc.gov/growthcharts/clinical_charts.htm)).

## ***Contains Nonbinding Recommendations***

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- 127 – In general, adolescents with body weight of less than 40 kg should switch to a body  
128 weight (mg/kg) or body surface area (mg/m<sup>2</sup>) adjusted dose. This adjusted dose  
129 should be based on an adult reference body size (e.g., the average adult body weight  
130 of 70 kg or median body weight or surface area of the adult patient population  
131 determined from existing data).  
132  
133

### **V. SAFETY MONITORING**

134 Safety data collected during the trial should be examined for any age-related differences.  
135

136 The evaluation of developmental toxicities (e.g., growth derangements, fertility issues) that  
137 require a long duration of follow-up may not be possible in the context of early phase trials;  
138 however, sponsors should develop a plan for longitudinal evaluation of potential developmental  
139 toxicities when it is feasible, particularly in trials enrolling patients in earlier lines of therapy.  
140  
141

142 Juvenile animal studies are not routinely needed before the enrollment of adolescents in  
143 oncology clinical trials, unless clinical and/or nonclinical data do not provide sufficient  
144 information on toxicities.<sup>4</sup>  
145  
146

### **VI. ETHICAL CONSIDERATIONS**

147  
148 Under 21 CFR 50.50, IRBs reviewing adult oncology clinical trials that allow for the enrollment  
149 of adolescents must ensure that the provisions of 21 CFR part 50, subpart D, Additional  
150 Safeguards for Children in Clinical Investigations, and, specifically, 21 CFR 50.52, Clinical  
151 investigations involving greater than minimal risk but presenting the prospect of direct benefit to  
152 individual subjects, are satisfied before approving the studies.  
153  
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155 Enrollment of appropriately selected adolescents in relevant adult oncology trials with  
156 appropriate dose considerations and adequate safety monitoring is justified given the severe and  
157 life-threatening nature of their disease.  
158  
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<sup>4</sup> 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.