August 3, 2018

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2018-D-1540: FDA Draft Guidance on Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance, Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's member companies take enormous risks every day to develop the next generation of biomedical breakthroughs for the millions of patients suffering from diseases for which there are no effective cures or treatments and BIO is proud of their innovative spirit and their dedication to alleviating human suffering.

BIO appreciates that the FDA developed Draft Guidance on Considerations for the Inclusions of Adolescent Patients in Adult Oncology Clinical Trials. We believe that the Draft Guidance is an important step towards ensuring that stakeholders, including Industry Sponsors and FDA reviewers, understand the FDA's expectations regarding the inclusion of adolescents in clinical trials for oncology products. Because the Draft Guidance signals the first time that a health authority memorializes the principles outlined in the Guidance (i.e., recommendation to enroll adolescents in adult oncology studies), we ask the FDA to consider reviewing and discussing the Draft Guidance with other global health authorities at upcoming pediatric cluster calls. Sharing and discussing the principles outlined in the Draft Guidance with other global health authorities serves as an important mechanism for ensuring global harmonization of the inclusions of adolescent patients in adult oncology clinical trials. Additionally, BIO also asks the FDA to consider educational efforts directed towards institutional review boards (IRBs), as successful implementation of the principles outlined in the Draft Guidance will rely upon agreement from IRBs.

BIO has included general comments below as well as specific line edits beginning on page three of this letter for the FDA's consideration.

General Comments:
BIO requests that the FDA consider clarifying how the Draft Guidance relates to provisions outlined in the Pediatrics Research Equity Act (PREA) and the FDA Reauthorization Act of 2017, Section 504, Development of Drugs and Biological Products for Pediatric Cancers. For example, if a sponsor enrolls adolescents in an adult trial according to the principles in this draft guidance, BIO asks the FDA to revise the Final Guidance to describe whether and when the PREA requirements for the adolescent age have been satisfied.

BIO also requests that the FDA consider including case examples in the final guidance demonstrating circumstances when adolescents have different physiology and/or psychology, relative to adults. For example, early clinical trials for oncology compounds often analyze electrocardiography interval data, however, electrocardiographic findings in adolescents are often not the same as the adult population and have unknown relevance to proarrhythmia potential. Greater clarity from the FDA regarding their expectations for the conduct of adult clinical trials that include adolescents when the physiology and/or psychology of the adolescents may be different from adults would aid in successful implementation of the principles outlined in the Draft Guidance. BIO also recommends that the Draft Guidance be enhanced by the addition of text that notes potential differences in clearance and drug-drug interactions between small molecules and biologics. Given that adolescent patients may be on concomitant medications such as anti-seizure medicines or vaccines, the Guidance should also acknowledge the potential for drug-drug interactions.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
Lines 38-39	The Guidance encourages sponsors to contact the responsible FDA review division to discuss details of the adult oncology drug program that includes adolescents before implementation. However, the Draft Guidance does not outlines a timeline by which such meetings should occur.	BIO requests that the Guidance state that sponsors discussions with FDA on the proposed inclusion of adolescents in adult oncology drug programs would occur within 30 days of a sponsor's request.
Lines 53-56	To clarify and enforce that there is a change to how the FDA will view the inclusion of adolescents in adult oncology clinical trials, BIO requests that the statements, "adolescents, because of their age, generally are not eligible for enrollment in adult oncology trials. . ." addresses the historical view that adolescents were note eligible for the trials.	BIO requests the following edit: "adolescents **have historically been ineligible due to age, even if medically appropriate,** for enrollment in adult oncology trials"
III. CRITERIA FOR INCLUDING ADOLESCENTS		
Lines 61-88	Data from several clinical trials analyzed by the FDA during 2012 a Clinical Pharmacology Advisory Board[1] concluded that clearance and dose in adolescents could be predicted accurately from adult data,	BIO requests that the FDA reference the 2012 Clinical Pharmacology Board determination and clarify the criteria for which adolescents could be enrolled in early dose cohorts.

[1] Food and Drug Administration, Center for Drug Evaluation and Research, Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology Summary, March 14, 2012.

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	however this information in not reflected in the Draft Guidance.	
Lines 63-66	As it is currently outlined, this section limits the kinds of cancers that could be relevant for both adult and adolescent patients.	BIO recommends the follow edit: "Adolescents should be eligible for enrollment in adult oncology clinical trials at all stages of drug development **based on non-clinical or clinical data indicating the target is potentially clinically** ~~**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."
Lines 72-74	Lines 72-74 of this section read as though adolescents are excluded from first in human studies. However, lines 77-82 read as though adolescents can be included in first in human studies, under certain conditions.	BIO suggests allowing the inclusion of adolescents in these trials if they fulfil the inclusion/exclusion criteria, as suggested in lines 80-82.
Lines 76-78	21CFR50.52 outlines three criteria, of which the first two are related to the dose/administration of the drug. These two criteria are important and should be clearly outlined in the Guidance.	BIO request the following edit: If adolescents are to be enrolled in early dose cohorts, sponsors should ensure that the dose to administered satisfies 21 CFR 50.52 (see section VI., Ethical 78 Considerations) **including the following:** **(a) The risk is justified by the anticipated benefit to the subjects;**

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		(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and" BIO also recommends that the third criteria should be added as a separate bullet under the relevant section of the Guidance: (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.
IV. DOSING RECOMMENDATIONS		
Lines 94-107	This section refers to the use of PK data for determining general dosing recommendations but the section does not refer to relevant PD data.	BIO suggests that the FDA consider adding information to this section regarding the collection of PD samples (if available/applicable) in adolescents to verify/confirm the same (similar) PK/PD relationship in adults. BIO requests the following edit: "The recommended dosing approach should be supported by the PK **(and PD, if applicable)** 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."
Lines 117-125	In this section, the FDA indicates that "An FDA analysis of adult population pharmacokinetics of oncology drugs suggested that 40 kg (the average body weight of a 12-year-old) is generally the lower	BIO requests that FDA include reference to factors such as mechanism of action, potential toxicities, and the modality of the drug in the section addressing dosing recommendations.

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	end of the body weight range that has no clinically relevant effect on drug pharmacokinetics or safety." This statement may be overly generalized. For example, cytotoxics, target therapies, and immuno-oncology therapies may involve other important, specific considerations.	
Lines 127-131	For clarity, the word "switch" in the current language (for drugs with fixed dosing) could be inferred to change dosing from fixed to adjusted during a patient's participation in the study.	BIO requests the following edit: "In general, adolescents with body weight of less than 40 kg should ~~**switch to**~~ **receive** 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)." BIO also requests that the FDA consider allowing sponsors to exclude adolescent subjects weighing less than 40 kg from non-pediatric safety and efficacy studies to be included or be enrolled in a sequential fashion after data from >40 kg adolescents are available.
Lines 127-131	This section refers to an example indicating the average adult body weight of 70Kg or median body weight or surface area of the adult patient population determined <u>from existing data</u>.	BIO requests that the FDA provide clarity as to whether the reference to 'existing data' refers to adult data from the trial or the adult patient population data in general.
IV. SAFETY MONITORING		
V. ETHICAL CONSIDERATIONS		
Lines 148-159	BIO believes the "ethical considerations" section could be strengthened and the utility of the Guidance	BIO requests that the FDA include recommendations in the "ethical considerations" section of the Draft Guidance to

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	increased, if this section were expanded to address FDA's recommendations (either directly or by reference) for contraception when adolescents are included in adult trials, particularly when the investigational drug is known to have effects on the reproductive system.	address the use of contraception when adolescents are included in clinical trials.