Biotechnology Innovation Organization

February 11, 2020

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

Re: Docket No. FDA–2019-D-4751: Food and Drug Administration Reauthorization Act Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding FDA's Draft Guidance on Implementation of Pediatric Studies of Molecularly Targeted Oncology Drugs.

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 members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO thanks FDA for the development of the Draft Guidance on FDARA Implementation for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Section 505B of the FD&C Act. It is essential that there is clear and comprehensive guidance for Sponsors on pediatric studies of molecularly targeted oncology drugs so that Sponsors can meet the requirements outlined in statute beginning in August 2020. BIO would like to address some key issues associated with interpretations of the underlying statute that are not entirely clear within the Draft Guidance. Two issues of note relate to the pediatric investigation under section 505B(a)(3), as well as the circumstances surrounding the deferral and/or waiver rules governing applications for drugs/biologics active against molecular targets on the substantial relevance list. We have previously raised these concerns in a letter to FDA's Office of Chief Counsel and we would like to reiterate our positions in an effort to clarify both issues in any resulting final guidance. Set forth below we elaborate on each of these issues more substantively and provide several additional recommendations that we believe will help strengthen and make sure clear the final guidance.

I. The Statute Contemplates Only One Molecularly Targeted Pediatric Investigation.

BIO notes that throughout the Draft Guidance the occasional use of the parenthetical (ies) as a common reference to the possibility of more than one clinical pediatric investigation and/or study. While never addressed specifically in the Draft Guidance, we believe FDA should clarify in the final guidance a position consistent with the statute that only one molecularly targeted pediatric investigation will be required for any one application and that only Pediatric Research Equity Act (PREA) or the new Section 504 study requirements can be imposed upon an individual application, not both.

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Specifically, where FDA has determined that the new investigation requirement applies to a particular original application, the Agency will require a sponsor to conduct only one molecularly targeted pediatric clinical investigation. Although FDA's determination of substantial relevance may be based on data from multiple preclinical or clinical investigations (*e.g.*, a collection of data from multiple studies), the statute requires the sponsor perform only one "molecularly targeted pediatric cancer investigation." Additionally, as addressed in our letter to FDA's Office of Chief Counsel, the statute does not mandate that a sponsor perform preclinical testing followed by clinical testing, and it does not authorize FDA to require multiple clinical investigations to satisfy section 505B(a)(3), either before approval or as postmarketing requirements.

Section 505B(a)(3)(A) describes "*the investigation," explaining that "the investigation . . . is a molecularly targeted pediatric cancer investigation, which shall be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling.*"[1]

The statute refers to the new investigation requirement in the singular and thus, contemplates that a sponsor must perform only one molecularly targeted pediatric cancer investigation where FDA determined that a target is substantially relevant to the growth or progression of a pediatric cancer. Indeed, the statute's use of the singular "investigation" and "study" stands in contrast to the use of the plural "investigations" elsewhere in the FDCA.[2] In further contrast, traditional PREA requires submission of "assessments" in the plural and suggests that FDA may require multiple studies to provide "data . . . that are adequate" to meet its requirements.[3] Traditional PREA also provides FDA with latitude to fashion study requirements to ensure that assessments "contain data . . . that are adequate . . . to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations" and "support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective."[4] Section 505B(a)(3) provides no such flexibility. Accordingly, sections 505B(a)(1)(B) and 505B(a)(3) authorize FDA to require a single study, not multiple studies, to satisfy the new investigation requirement.[5] We ask that final guidance on this topic clarify and confirm this position.

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[1] *FDCA* § 505B(a)(3)(A) (emphasis added).
[2] *See id.* § 505(d) ("'[S]ubstantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations . . . .").
[3] *Id.* §§ 505B(a)(1)(A), 505B(a)(2); *id.* § 505B(a)(2)(B)(ii) ("A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.").
[4] *Id.* § 505B(a)(2).
[5] *Cf. Russello v. United States,* 464 U.S. 16, 23 (1983) ("[W]here Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." (citations omitted)). The use of the plural "investigations" in sections 505B(a)(3)(B) & (C) does not change this conclusion. These provisions use the plural to confirm that FDA has the same authority to extrapolate and defer and waive study requirements *for all drugs and biologics* under traditional PREA and section 505B(a)(3).

II. FDA May Not "Defer" the New Investigation Requirement if the Agency Has Not Determined Substantial Relevance.

Separate from considerations surrounding application of the study requirements, another aspect of the Draft Guidance that requires clarification is the issue of deferrals. This topic is not clearly articulated in the Draft Guidance and, as such, we request that FDA clarify that it may only defer the new investigation requirement with respect to an original application for a new active ingredient if it is first established that a molecular target is substantially relevant to the growth or progression of a pediatric cancer.

A recent presentation by an Office of Hematology and Oncology Products official suggested that deferral of the new investigation requirement may be considered if, among other things, there are "insufficient data to define relevance" to a pediatric cancer.[6] For three reasons, however, the statute does not permit FDA to defer its substantial relevance determination with respect to an original application for a new active ingredient until after that application's submission or approval.

First, this approach would be incompatible with the deferral provisions. Section 505B(a)(4)(A) authorizes FDA to "defer submission of some or all assessments *required under* [traditional PREA] or reports on the investigation *required under* paragraph (1)(B) [*i.e.*, the new investigation requirement] until a specified date after approval" of the product if one of the deferral criteria is met.[7] Thus, the statute enables FDA to defer an already-applicable statutory requirement to submit pediatric study data; it does not authorize the Agency to postpone its determination as to what study requirements apply. Indeed, in the context of traditional PREA, FDA has not interpreted the deferral criteria to permit it to defer deciding whether traditional PREA applies to an application until after approval. Instead, the approval letter for a drug with deferred PREA requirements specifies those deferred study requirements. And the statute makes clear that deferrals and waivers apply to the new investigation requirement "to the same extent and in the same manner as such deferrals and waivers apply with respect to the assessments under" traditional PREA.[8] In sum, the statute does not contemplate or authorize deferral of a decision about the applicable statutory testing requirements under after submission or approval of an application.

Second, "deferring" the decision as to which pediatric testing requirements apply to an original application until after the application's submission or approval would depart from the text of sections 505B(a)(1)(A) and 505B(a)(1)(B). Both provisions mandate that sponsors "shall submit *with* the application" the pediatric data required under traditional PREA or the new investigation requirement, as applicable.[9] Indeed, FDA's Manual of Policies

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[6] Nicole Drezner, Pediatric Oncologist, Office of Hematology & Oncology Products, FDARA Implementation: Future Pediatric Cancer Drug Development *available at* https://www.fda.gov/media/122696/download.

[7] FDCA § 505B(a)(4) (emphasis added).

[8] *Id.* § 505B(a)(3)(C).

[9] *Id.* § 505B(a)(1)(A) ("[A] person that *submits*, on or after the date of the enactment of the Pediatric Research Equity Act of 2007, an application (or supplement to an application) for a drug [under section 505 of the FDCA or section 351 of the Public Health Service Act] for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration . . . shall *submit with the application* the assessments described in [section 505B(a)(2)].") (emphasis added)

and Procedures provides that FDA may refuse to file a marketing application if it contains incomplete pediatric assessment data (in the absence of a deferral or waiver request), underscoring that the decision about the applicable pediatric testing statute is not a post-submission or post-approval issue.[10] Likewise, section 505B(a)(1)(B) refers to an original application for a new active ingredient. Thus, the new investigation requirement cannot apply to submissions made after the original application (which would be amendments) or to those made after approval, when the drug would no longer contain a new active ingredient. Accordingly, applying the new investigation requirement to a drug after submission of an original application for that drug would be incompatible with sections 505B(a)(1)(A) and 505B(a)(1)(B).

Finally, this approach would conflict with the statutory provision on iPSPs. Under section 505B(e)(2)(A) of the FDCA, an applicant subject to PREA must submit an iPSP before it submits the required assessments and not later than 60 calendar days after the date of the end-of-phase 2 meeting or such other time as may be agreed upon between the Secretary and the applicant.[11] PREA mandates that the plan must contain "an outline of the pediatric study or studies that the applicant plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach)," as well as requests for deferral or waiver.[12] Thus, the statute contemplates that the sponsor must develop its iPSP based on some understanding of the required investigations for its drug—including, post-FDARA, whether the sponsor must generate pediatric assessments in the claimed adult indication or conduct a molecularly targeted pediatric cancer investigation in potentially unrelated indications. It is infeasible for sponsors to prepare pediatric study outlines if they do not know which disease they must study or the objectives of the study. Moreover, given that the pediatric study data generally must be submitted "with" the application, determining whether traditional PREA or the new investigation requirement applies at the iPSP stage will best enable submission of the reports with the application. This approach therefore best accords with the statute. In contrast, a "deferral" of the decision as to which statutory framework applies to an application until after submission or approval of an original application is incompatible with these provisions.

We acknowledge that, under traditional PREA, the Agency has not considered decisions regarding the scope of pediatric investigations made at the iPSP stage as binding.[13] Given the significant amendments of FDARA, however, we believe that earlier decision-making on

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(footnote omitted); *id.* § 505B(a)(1)(B) ("A person that *submits*, on or after the date that is 3 years after August 18, 2017, an original application for a new active ingredient . . . shall *submit with the application* reports on the investigation described in paragraph (3) if the drug or biological product that is the subject of the application is . . . directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer.") (emphasis added).

[10] *See* FDA, MAPP 6025.4, Good Review Practice: Refuse To File (Revised Sept. 5, 2018), at 18.

[11] FDCA § 505B(e)(2)(A).

[12] *Id.* § 505B(e)(2)(B).

[13] *See*, *e.g.*, FDA, Draft Guidance for Industry, *How to Comply with the Pediatric Research Equity Act* at 12 (Sept. 2005); FDA, Draft Guidance for Industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* at 10 (Mar. 2016).

pediatric study requirements in the oncology context is not only warranted but most consistent with the statutory provisions as explained above. We firmly believe that the process of determining whether traditional PREA or the new investigation requirement applies to a product should be time-bound for successful implementation of FDARA and to expedite and streamline the development of important cancer medicines for patients.

In particular, we are concerned about the potential for the applicable pediatric testing requirements to remain open after approval based on the rationale that FDA might one day decide new data establish substantial relevance. If FDA kept open the possibility of imposing the new investigation requirement at any time, there would be significant uncertainty for stakeholders. Instead, FDA should make the decision regarding the applicable pediatric study requirements by the time the iPSP is due. As is done now, FDA should memorialize that decision in the later BLA or NDA approval letter. Our suggested approach will provide an organized and coordinated process for the implementation of FDARA and avoid delays that could result from the application of the new investigation requirement late in the development process. For the reasons explained above, we request that the final guidance confirm that the Agency will not defer the new investigation requirement based on a conclusion that FDA has not determined whether or not substantial relevance has been established beyond the period of review of the NDA/BLA, but instead will apply traditional PREA in this scenario.

III. Need for Opportunities for Discussions Regarding Global Development Programs.

BIO appreciates the Agency's acknowledgement of the struggle that the industry faces in attempting to work through thousands of candidate molecules to identify which should be studied in pediatric cancer where patient populations are limited. However, we remain concerned that there has not been enough attention paid to the needs of the innovative drug development industry to find a pragmatic solution to balancing the needs for "early" investigation of investigational agents for pediatric cancer patients all-the–while balancing the overly competitive landscape and the certain wastage of valuable patients in studies that will never properly inform on effective use of our therapeutic agents. The FDA references the Pediatric Cluster Teleconferences, the Common Commentary Process, as well as formal Parallel Scientific Advice as possible mechanisms to address the above challenge. However, Drug Developers have, on several occasions, raised concern about the insufficiency of the existing regulatory pathways to engage the broad set of international agencies in a scientific manner that meets both the agency and Industry needs. While the Pediatric Cluster Meetings and Common Commentary Process provide an important avenue for regulators to discuss pediatric programs and studies, the Pediatric Cluster Meetings and Common Commentary Process do not address the needs of Industry so that Industry can more quickly deliver therapies to pediatric patients. Specifically, Industry is rarely made aware of nor permitted to be present when Pediatric Cluster discussions occur, which means the opportunity for real-time dialogue with global health authorities is lost.

For Parallel Scientific Advice meetings there is a rigorous selection process for participation and our members report that the process for requesting and obtaining this advice is extremely time intensive for both the regulators and sponsors. As a result, it is a tool that has been rarely utilized and is thus of limited value for achieving international scientific

consensus on any development programs, including those for pediatric oncology indications on a routine basis.

BIO encourages FDA to continue their dialogue with other agencies (i.e., EMA) to find a consistent pathway that can be utilized routinely by sponsors (particularly of pediatric oncology development programs) to seek timely binding, aligned advice from more than one regulatory agency, as appropriate. Establishment of such a pathway will significantly enhance the agreement process by making the best use of limited regulator resources, providing real resource efficiencies, and more certainty around the processes for agreeing pediatric plans. Importantly, these processes will speed the delivery of important therapies to pediatric patients.

IV. Additional Comments.

BIO generally agrees that a specific or minimum evidence standard for determining target relevance is difficult from a scientific perspective for the reasons stated by the FDA. However, from an ethics perspective pediatric clinical studies involving more than a minor increase over minimal risk must offer the prospect of direct benefit to individual pediatric patients in the trial as outlined in subpart D, 50.52.[14] Additionally, in the Draft Guidance, FDA indicates that "*One or more of the following may, as appropriate, inform FDA's determination that a molecular target is substantially relevant for purposes of section 505B:"* and then lists a series of circumstances. However, the list of circumstances under which a target may be considered substantially relevant is not consistent with the need to provide "*evidence that addressing the molecule (i.e. target) with a drug produces a predictable therapeutic effect*..." as written on lines 129-130. This evidence of (most often preclinical) target drug modulation may not always be necessary to consider a pediatric plan.

BIO appreciates that throughout the Draft Guidance FDA emphasizes opportunities for FDA and Sponsors to engage in early meetings on pediatric oncology programs. However, to make the best such of such discussions BIO requests that FDA provide additional detail in the final version of the guidance regarding what information and/or data, if available, sponsors should bring to such discussions with the FDA.

BIO also appreciates that the Agency is attempting to avoid imposing a requirement to conduct duplicative studies in a highly competitive development space for rare pediatric cancers. We are, however, concerned about the potential for unintended consequences that may result from the approach as proposed in lines 404-409 of the Draft Guidance. BIO would welcome the opportunity to discuss these concerns with the Agency in more detail and to work constructively and collaboratively with the Agency to identify an alternate way forward or potential pilot to be tested before the guidance is finalized.

In addition, BIO requests that FDA provide further discussion and greater clarity in the final guidance as to the meaning of "generation" and "class" as these terms are used in line 404

[14] 21 CRF 50.52. Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

of the Draft Guidance. For example, it would be helpful for the final guidance to indicate when and on what basis the Agency will make the determination of a molecule's generation or class. Alternatively, if the expectation is that the sponsor will make these determinations and submit them to the Agency for concurrence, information about how Agency personnel will assess these submissions, including the criteria against which sponsor assertions of generation or class will be judged, would be helpful.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance on Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
John A. Murphy, III
Vice President
Deputy General Counsel
Biotechnology Innovation Organization

/S/
Danielle Friend, Ph.D.
Senior Director, Science and Regulatory Affairs
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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
Line 47	In this section the FDA indicates that "*Specifically, if an original NDA or BLA is for a new active ingredient, and the drug that is the subject of the application is intended for treatment of an adult cancer and directed at a molecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, reports on the molecularly targeted pediatric cancer investigation required under section 505B(a)(3) of the FD&C Act must be submitted with the marketing application, unless the required investigations are waived or deferred.*"	BIO requests that the FDA consider adding a link to Section III D after "reports" so that it is clear what is meant is the results of the pediatric investigation.
Line 53	In this section FDA indicates that "*Timely investigation in pediatric patients of the antitumor activity of potentially effective targeted drugs under development in adults, and of those drugs' toxicities relative to the unique growth and developmental considerations of pediatric patients, is intended to accelerate early pediatric evaluation of these products and ultimately facilitate development of appropriate new therapies for pediatric patients,*" The goal of FDARA Section 504 is timely investigation of safety PK and Preliminary efficacy, not antitumor activity.	BIO believes that this section should focus on intent of the law which is investigate safety, PK, and preliminary efficacy to accelerate early pediatric evaluation, to this end, we request the following edits: "*Timely investigation in pediatric patients* ~~***of the antitumor activity***~~ *of potentially effective targeted drugs under development in adults, and of those drugs' toxicities relative to the unique growth and developmental considerations of pediatric patients, is intended to accelerate early pediatric evaluation of these products and ultimately facilitate development of appropriate new therapies for pediatric patients.*"
III. REGULATORY CONSIDERATIONS		

SECTION	ISSUE	PROPOSED CHANGE
A. Molecular Target		
Lines 129-131	In this section, the FDA indicates that *"For a molecule to be considered a molecular target for purposes of section 505B, there should be evidence that addressing the molecule with a drug produces a predictable therapeutic effect resulting in alteration of the disease process."* However, the above definition of molecular target is problematic because companies develop drugs to molecular targets that they hope will "produce a predictable therapeutic effect resulting in alteration of a disease process," but this is not known until after many years of research when some drugs are approved for marketing and others fail. Additionally, by using this definition of molecular target the FDA seems to limit the application of section 504 only to oncology drugs that have already been approved, which seems counter to the intent of the law. "Predictable therapeutic effect" also raises the question of whether this effect is in adults or children, and if the latter, why are further studies needed. Additionally, it is unclear as to whether "molecule" refers to "molecular target". It is also unclear as to how the FDA determines "predictable"?	BIO request that the FDA consider the following edit: "For a molecule to be considered **to be aimed at a** molecular target for purposes of section 505B, there should be evidence that addressing **(i.e., binding to, interacting with)** the ~~**molecule**~~ **molecular target** with a drug produces a **physiologic response that results in a desirable effect against a cancer either in vitro, in vivo or in clinical settings.**" BIO also request that the FDA provide clarity, either qualitative or quantitative or via an example for illustration, what is meant by "predictable".
B. Factors Considered in the Determination of Relevance		
Lines 133-216		BIO is concerned that Sponsors who are less familiar with FDARA Section 505B PREA have indicated that the guidance does not provide clear guidance on what to do regarding investigational agents which work through a molecular target

SECTION	ISSUE	PROPOSED CHANGE
		that is not listed by the Agency on either list. BIO requests that the FDA provide additional detail to clarify this point.
Lines 139-145	In this section the FDA indicates that "*One or more of the following may, as appropriate, inform FDA's determination that a molecular target is substantially relevant for purposes of section 505B:*" and then lists a series of circumstances. However, the list of circumstances under which a target may be considered substantially relevant is not consistent with the need to provide "*evidence that addressing the molecule (i.e. target) with a drug produces a predictable therapeutic effect*..." as written on lines 129-130. This evidence of (most often preclinical) target drug modulation may not always be necessary to consider a pediatric plan.	BIO requests that the FDA address this inconsistency included in the current version of the guidance.
Lines 141-142	In this section the FDA indicates that "*Molecular targets that lack sufficient evidence for FDA to determine whether they are "substantially relevant" or "not substantially relevant" will not be included in a target list, however, the lists will be updated regularly to reflect additional determinations regarding the relevance of molecular targets.*"	BIO requests that the FDA indicate how often the lists will be updated and also indicate any opportunities for the public to make comment or provide feedback on the list of targets. BIO believes that the lists should be updated annually and the update be completed through a public, transparent process that includes the opportunity for interested stakeholders (e.g., academia, regulators, industry and patient representatives) to provide data and comments that are considered prior to the publication of the list. This process should include proposed changes, a public comment period regarding the suggested changes, a public workshop/meeting, followed by publication of the draft list in the federal register, reflecting input received during the public comment period and public workshop/meeting with opportunity for public comment prior to final publication.

SECTION	ISSUE	PROPOSED CHANGE
Lines 144-148	The guidance states "*One or more of the following may, as appropriate, inform FDA's determination that a molecular target is substantially relevant for purposes of section 505B."* It then lists as the first factor: *"The target has been identified in a cancer which occurs in pediatric patients. For targets within a cancer cell lineage, the target is intrinsically or differentially expressed in the cancer of interest compared to normal site-specific tissues."* This factor, on its own, does not meet the Agency's previously stated position (Lines 129 – 130) that for a molecule to be considered a molecular target for purposes of 505B, " *... there should be evidence that addressing the [molecular target] with a drug produces a predictable therapeutic effect resulting in alteration of the disease process."*	BIO believes that the mere presence of a molecular target in a pediatric cancer, should not be the sole characteristic that defines whether a drug or biologic is aimed at a target that is "substantially relevant" to the growth and progression of a pediatric cancer. "Substantial relevance" should be supported by a compendium of data for a specific pediatric cancer, including the following, if available: • Robust and high-quality evidence that the molecular target is expressed in the specific pediatric cancer, in cells of the micro-environment of the pediatric cancer, or in immune cells that may target the pediatric cancer in some way; • Robust and high-quality evidence that the molecular target is biologically active/functional in the same pediatric cancer, in cells of the micro-environment of the pediatric cancer, or in immune cells that may target the pediatric cancer in some way; • Robust and high-quality evidence (to the extent possible) in nonclinical models for the specific pediatric cancer, preferably in vivo models, in which disrupting/affecting the molecular target (usually via a drug/biologic) produces a substantial effect on the growth or progression of a pediatric cancer; • Robust and high-quality data from adult patients demonstrating at least preliminary relevant safety and efficacy. • For the second and later drugs and biologics targeting the same molecular target, positive results from pediatric trials and/or positive clinical experiences with drugs and biologics with the same target may also support a

SECTION	ISSUE	PROPOSED CHANGE
		determination of "substantial relevance" for the molecular target to the specific pediatric cancer studied. BIO also request the following edit: "~~**One or more of the following may, as appropriate, inform**~~ FDA's determination that a molecular target is substantially relevant for purposes of section 505B **will be determined using the totality of evidence which may include:**…"
Lines 161-165	In this section the FDA indicates that "*In vitro or in vivo activity of drugs in combination: When single agents do not result in target modulation, support for substantial relevance may be found in evidence for additive or synergistic activity when an agent which effects target modulation is used as part of a biologically rational combination in appropriate model systems.*"	BIO suggests that FDA consider including a separate section with more detail on pediatric regulatory considerations for clinical development for two or more investigational drugs (e.g., co-development of novel-novel drugs) for the treatment of adult cancers that are directed at a molecular target in a pediatric cancer. If applicable, the FDA should also cross-reference existing guidance documents on this issue (i.e. Guidance to Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination) for guiding principles.[15]
Lines 169-172	In this section FDA indicates that "*Biomarkers expressed by tumor cells of cancers that occur in pediatric patients and that may predict response to target modulation may contribute to the concept of substantial relevance and also be useful in selection of the appropriate pediatric study population.*"	BIO request that FDA provide more information as to how biomarkers may inform substantial relevance for pediatric cancers, as in the context of adult development programs, FDA requires evidence that biomarkers are relevant and/or are directly associated with efficacy.

[15] FDA Final Guidance on Codevelopment of Two or More New Investigational Drugs for se in Combination.

SECTION	ISSUE	PROPOSED CHANGE
Lines 176-177	In a 2016 report from the Biomedtracker (2006 – 2015), Oncology drugs (n = 3163) had the lowest likelihood of approval from Phase I (only 5.1%) of all the major disease areas. Given this, it is our perspective that the Agency's request for "... *every effort to initiate pediatric non-clinical investigations early in the development timeline*" is inconsistent with making efficient use of resource in early oncology drug development. In addition, this is applicable only when a relevant pediatric disease model is available and reasonably validated. We believe that this is an area where the academic/research community is expected to make contributions to ensure enhancements to the quality of pediatric non-clinical testing. While we fully support the statement made in Lines 174 – 175, we believe that the language in Line 176 – 177 should be modified to reflect the reasonable ability of the investigational drug development community.	BIO requests the following edits: "Therefore, ~~every~~ effort should be made to initiate pediatric non-clinical investigations early in the development timeline**, when appropriate**." OR "Therefore, ~~every~~ effort should be made to initiate pediatric non-clinical investigations early in the development timeline **whenever a relevant pediatric cancer model is available**." BIO also suggest that when such a model does not exist, the guideline should clarify that the development and validation of new preclinical models are beyond the scope of the regulatory guidelines.
Lines 179-183	In this section FDA indicates that "*FDA may determine available evidence demonstrates that a molecular target is not substantially relevant to the growth or progression of pediatric cancer based on, for example, the absence of a biologic rationale for a specific target's function as an oncogenic driver, or a lineage associated target that is not a component of a pediatric cancer cell, or pre-clinical data that demonstrates no tumor cell growth effect by inhibition of the target.*"	The last part of this section indicates that non-clinical data may provide evidence for a waiver request for a target that is on the "relevant molecular target list." To this end, BIO requests that FDA provide additional detail regarding recommendations for such non-clinical studies (e.g., how many models should be evaluated to determine "no tumor cell growth effect").

SECTION	ISSUE	PROPOSED CHANGE
C. Target Lists		
1. The relevant molecular target list		
2. The non-relevant molecular target leading to waiver list		
Lines 211-214	Per the current version of the guidance, it is unclear as to whether the Agency envisions a situation in which a full iPSP waiver is granted for a product because the molecular target appears on the Non-Relevant Molecular Target List, but subsequently the molecular target is re-classified as "Relevant", or, is removed from the aforementioned list.	BIO believes that if a waiver is granted for a product because the molecular target appears on the Non-Relevant Molecular Target List and subsequently the molecular target is re-classified as "relevant" or is removed from the aforementioned list, the issues waiver will remain a waiver for the pediatric studies. BIO requests that FDA make this clear in the updated version of the Draft Guidance.
D. Content of the Initial Pediatric Study Plan (iPSP) and Description of Recommended Studies		
Line 221	In this section FDA indicates that "*Section 505B(e) of the FD&C Act requires applicants subject to PREA to submit an initial pediatric study plan prior to the submission of an NDA or BLA.*"	For clarity, BIO requests the following edits: "~~**Section 505B(e) of the FD&C Act requires applicants subject to PREA to submit an initial pediatric study plan prior to the submission of an NDA or BLA.**~~" "**A sponsor should not submit a marketing application or supplement until agreement has been reached on the iPSP.**"
Line 227	In this section FDA indicates that "*An extensive list of cancer diagnoses occurring almost exclusively in adults thus is included in a list of adult-related conditions that qualify for a waiver because they rarely or never occur in pediatrics.*"	BIO requests that the "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" list (on FDA website) be updated to indicate that it is only relevant to supplements filed after Aug-2020 and drugs that do not fall under FDARA section 504.
Line 236	In this section the FDA indicate that Submission ... "*must include reports*" of ... pediatric cancer investigations.... In many cases, such "reports" may not yet be available at the time of the first adult	BIO requests the following edit: "Therefore, original applications for a new active ingredient that are submitted on or after August 18, 2020, and for

SECTION	ISSUE	PROPOSED CHANGE
	submission, particularly in cases of accelerated development plans.	which the drug that is the subject of the application is intended for the treatment of an adult cancer and is directed at a molecular target determined to be substantially relevant to the growth or progression of a pediatric cancer must include **an updated iPSP and available** reports of molecularly targeted pediatric cancer investigations (which were described in an iPSP under section 505B(e) of the FD&C Act), unless a deferral or waiver is granted.[16] Sponsors are advised of the opportunity to seek early interaction with FDA to address their pediatric development.
Lines 238 - 240	In this section the FDA indicates "*Sponsors are advised of the opportunity to seek early interaction with FDA to address their pediatric development. Questions can be addressed to the Pediatric Oncology Program in the FDA's Oncology Center of Excellence.*"	BIO requests that the FDA cross-reference this section with lines 305-317. Additionally, it would be of value to have the Agency provide clarity on the 'Type' of meeting that may be utilized for such discussions.
1. iPSP Content		
Line 259	In this section FDA indicates that "Non-clinical proof-of-concept studies; planned and completed" should be included in the iPSP."	FDARA Section 504 does not require non-clinical studies. For clarity, BIO requests the following edit: "Non-clinical proof-of-concept studies **for the adult development program, if relevant**; planned and completed" should be included in the iPSP."
Line 261	In this section the FDA outlines content that should be included in iPSPs. The FDA indicates that the Sponsor should include any "Planned pediatric clinical	BIO requests the following edit: Planned pediatric ~~**clinical**~~ preliminary efficacy study~~**(ies)**~~

[16] See section 505B(a)(1)(B) of the FD&C Act.

SECTION	ISSUE	PROPOSED CHANGE
	study(ies) x Timeline of pediatric development plan," however, the statute requests "... dosing, safety, and preliminary efficacy to inform potential pediatric labeling," not clinical study(ies), therefore, it would seem that asking for "*Planned pediatric clinical study(ies)"* goes beyond what the scope of the law requires.	
2. Description of recommended studies to be included		
Line 277	In this section FDA indicates that "*Objectives of the studies described in the iPSP under section 505B(e) of the FD&C Act should include… Definition of the pediatric Recommended Phase 2 Dose(s) (RP2D).*" However, scheduling of immune oncology or genomically targeted therapies may be especially critical in the pediatric population and may enhance the tolerability profile of a given agent in this population.	BIO recommends the following text revision: Definition of the pediatric Recommended Phase 2 Dose(s) **and Schedule.**
Line 278-281	In this section FDA indicates that "*Assessment of activity (defined as overall response rate (ORR)) across the entire study population, in biomarker enriched population(s), in pre-specified disease cohorts, or in adaptive design settings, successively opened disease cohorts as evidence of activity warrants.*"	Preliminary efficacy as outlined by the statute was not intended to include ORR. To this end, BIO requests the following edit" "*Assessment of activity (~~defined as overall response rate (ORR)) across the entire study population~~, in biomarker enriched population(s), in pre-specified disease cohorts, or in adaptive design settings, successively opened disease cohorts as evidence of activity warrants.*"
Lines 281-282	In this section, the FDA indicates "*Assessment of activity (defined as overall response rate (ORR)) across the entire study population, in biomarker*	BIO requests that FDA clarify the boundary between what leads to a PSP and PPSR. BIO requests that the FDA expand a section of the guidance to address PPSRs, including

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	enriched population(s), in pre-specified disease cohorts, or in adaptive design settings, successively opened disease cohorts as evidence of activity warrants;" however, disease cohorts as activity warrants should be considered as part of a PPSR/WR.	reference to earlier discussions between the FDA and Sponsors on the PPSR in parallel with iPSP. Additionally, sample sizes for potential studies are likely to be low, especially considering the need for a placebo arm in some instances. Therefore, additional information on use of historical data and/or the role for Bayesian statistics should be included here. Reference to existing applicable Guidance on these topics would also be welcome within the footnotes as well.
Line 283-287	In this section FDA indicates that "*Factors to consider should include the frequency of the molecular target expected across pediatric cancers in general and/or within a specified histology or sub-type, the number of dose levels to be evaluated to identify a recommended pediatric dose, and statistical considerations including estimated response rate that would support further development,*" in some circumstances the numbers of patients included in studies will be too small to provide statistically significant differences.	BIO requests that FDA acknowledge that in some circumstances the number of patients included in studies will be too small to provide statistically significant differences.
Lines 297	In this section the FDA indicates that "*Early in the development of the iPSP, sponsors are encouraged to collaborate and seek advice from recognized subject matter experts, including those involved in clinical trial networks and academic investigators, to develop an appropriate non-clinical rationale for the iPSP and to facilitate scientifically rigorous study designs in clinically relevant diagnoses or subgroups of patients with the same diagnosis, or groups defined by*	BIO request that the FDA consider referring to the role for consortia that are available to inform clinical development in addition to academic investigators (e.g., NCI-PPTC, IMI2-ITCCP4, potential FNIH, among others).

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	biomarker detection of the target of interest irrespective of specific diagnosis."	
3. Early advice on pediatric development meetings for oncology projects subject to the amended provisions of section 505B of the FD&C Act		
Lines 304 – 316, lines 238-240	In this section the FDA refers to the use of the new meeting opportunity pertaining to pediatric drug development programs. We note, however, that these meetings are not limited to pediatric cancer programs but are intended to " *... if requested by the applicant with respect to a drug or biological product that is intended to treat a serious or life-threatening disease or condition, ...".* There are numerous serious or life-threatening disease or conditions in pediatrics which also will benefit from the ability to meet with the Agency early in development.	BIO requests that FDA include in other guidance beyond this Draft Guidance reference to these new meeting types, as they are appliable to development programs beyond oncology. In addition, BIO requests that FDA make explicit reference in the text to the relevant statute (Section 503B(e)(2)(c)(i)(1) of the Food Drug and Cosmetic Act). BIO also requests that FDA clarify that in addition to these meeting opportunities being available to all therapeutic areas beyond oncology, FDA should indicate that the early interactions are also available via all FDA divisions, not just oncology via the OCE. BIO believes that requests should not go to OCE if these meetings are open to other therapeutic areas, beyond oncology.
E. Additional Considerations for Rare Cancers		
Lines 319-328	In this section the FDA indicates that in the context of rare cancers in particular, innovative clinical trial designs should be considered.	BIO requests that the FDA expand upon this section or create a new section of the guidance to include reference to specific innovative designs and approaches such as use of real-world evidence, use of modeling/simulation approaches, and employing digital health tools to promote efficient pediatric studies. The FDA may consider referencing to other FDA guidance addressing the innovative approaches mentioned above.
1. Pediatric cohorts in existing adult trials		

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Line 331	In this section the FDA indicates that "*When a target being investigated in an adult clinical trial also occurs in a specific pediatric tumor(s), sponsors may consider including a pediatric cohort during the expansion phase of a clinical trial.*"	BIO requests the following edit: "*When a target being investigated in an adult clinical trial also occurs in a specific pediatric tumor(s), sponsors may consider including a pediatric cohort during the* ***initial or*** *expansion phase of a clinical trial.*"
2. Embedded pediatric trials		
3. Adolescent patients		
Lines 349-358	In this section FDA indicates that "*Inclusion of adolescents in adult trials would allow those patients access to investigational drugs with potential for benefit and generate clinical trial data in this population that could be included in prescribing information for safe and effective use at the time of approval. In some instances, efficacy in adolescent patients may be extrapolated from adult data; however, adequate approaches to evaluate safety in this population are required.*"	BIO requests that FDA clarify whether there can be overlap between the embedded pediatric trials and adolescents to confirm that the adolescent subgroup can be part of required pediatric studies.
4. Tissue/histology agnostic development		
5. Master protocols		
F. Consideration for Planned Waivers and Deferrals		
Lines 386-388	In this section FDA indicates that "*Deferral of a pediatric study may be appropriate when there is uncertainty regarding the single agent activity of a drug until such time that one or more biologically rational combinations demonstrates a clinical effect.*"	BIO requests that FDA clarify that at time of NDA/BLA submission the FDA will make the determination as to whether the single agent should be deferred. Additionally, BIO reiterates that even in the context of combinations, the FDA should make the final determination as to whether a single agent should be deferred at the time of NDA/BLA approval.
1. Deferral		

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Lines 404-421	The statute notes (Sec 504)(a)(1)(3)(C) "*Deferrals and waivers under paragraphs (4) and (5) shall apply to investigations described in this paragraph to the same extent and in the same manner as such deferrals and waivers apply with respect to the assessments under paragraph (2)(B).*'' Therefore, we are concerned that this guidance does not reference the existing means of deferral under the law, which include: - ''*(I) the drug or biological product is ready for approval for use in adults before pediatric studies are complete;* - *(II) pediatric studies should be delayed until additional safety or effectiveness data have been collected; or* - *(III) there is another appropriate reason for deferral*". Is it the Agency's position that the 3 'new' deferrals listed in the guidance are examples of what is meant under the law by "*there is another appropriate reason for deferral*"? If so, this should be clarified within the Guidance, and it should be made clear that the 3 existing deferral criterion should be the basis for a deferral request. If not, the guidance should clarify how these new deferrals are to be considered in relation to the existing deferral criterion under the law.	BIO requests that the Agency indicate that the 3 "new" factors for deferrals listed in the Draft Guidance are examples of what is meant under the law by "*there is another appropriate reason for deferral*". BIO requests that this be clarified within the Draft Guidance and it should be made clear that the 3 existing deferral criterion should be the basis for a deferral request.
2. Waivers		
	In this section FDA indicates that "*A waiver may be appropriate for the third or later generation/same in*	Per the proposal put forward by FDA in the Draft Guidance, if a later in class agent has no anticipated differential profile to

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	class product (with identical mechanism of action) when ongoing competing studies in the pediatric population are being conducted and when there is no convincing evidence that the new drug provides a superior pharmacologic, toxicity, or activity profile to the same in class product(s) already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation."	the preceding agents, they may be eligible for a waiver. BIO requests FDA to provide detail as to how BPCA would be addressed for a sponsor who receives a waiver in this instance. BIO believes that if a Sponsor receives a waiver or deferral, completion of pediatric studies should be left to the discretion of the Sponsor.
IV. GLOBAL IMPLICATIONS AND INTERNATIONAL COLLABORATION		
A. Pediatric Cluster Teleconferences		
Lines 443-444	In this section the FDA does not list the contact information for submitting a pediatric cluster request. If this section of the guidance is to be retained, consider adding expanding the activities of this pathway to improve its utility	BIO requests that the FDA add contact information for Sponsors to use when requesting drug product be considered for discussion on pediatric cluster teleconference. BIO also requests the follow edit: Sponsors also can submit a request to either the FDA or EMA that their drug product **or more generally, the appropriateness of potential indications by drug class** be considered for discussion.
B. Common Commentary Process		
Entire section	In this section the FDA does not list the contact information for submitting request for common commentary.	BIO requests that the FDA add contact information for Sponsors to request or ask questions about the common commentary process. BIO also requests that FDA provide additional information within the Draft Guidance that provides insights into the process that may be taken by sponsors to seek written

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		clarification or teleconference follow-up on the non-binding feedback received.
C. Formal Parallel Scientific Advice (PSA)		
Lines 461-477	In this section FDA refers to the Parallel Scientific Advise pathway as a mechanism for provision of concurrent exchange of advice from EMA assessors and FDA reviewers with sponsors on scientific issues to optimize drug development.	BIO requests that FDA provide more detail in this section on the PSA process, in particular, the timing relative to submission of an iPSP and a Pediatric Investigation Plan (PIP).