



February 9, 2015

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

Re: Docket No. FDA-2013-D-1275: Draft Guidance for Industry on General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry entitled "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products."

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 members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

GENERAL COMMENTS:

BIO greatly appreciates the Agency's work to publish this Draft Guidance. There are several aspects of the Draft Guidance for which BIO respectfully requests additional information or clarification.

A. Biologics Considerations

Although the scope of this Guidance is intended to include biologics, there is no clear definition of "drug" in the Draft Guidance, little mention of biologics in some sections of the Draft Guidance, and most of the references contained within the Draft Guidance pertain to small molecules. BIO recommends FDA including additional consideration of biologics and provides references that specifically discuss them. BIO also recommends further discussion of additional considerations, such as relevance of multiple species for complex targeted agents (*e.g.*, antibody drug conjugates) and similarities or differences in target abundance/expression between adults and pediatrics.

B. Clinical Pharmacology Considerations

BIO requests further discussion of specific strategies for Sponsors to approach clinical pharmacology considerations (such as developmental maturation of absorption, distribution,



metabolism, and excretion [ADME] determinants) in Section III. A decision tree and algorithm on the molecular types and other basic pediatric clinical pharmacology considerations (including modeling and simulation approaches) could help Sponsors inform the path forward.

BIO also believes that the Guidance would benefit from a clearer and more detailed explanation of the fundamental principles governing the use of pharmacokinetics (PK) and pharmacokinetics/pharmacodynamics (PK/PD) for bridging from adults to pediatrics. The three approaches for providing substantial evidence to support the safe and effective use of drugs in the pediatric population assume similarities in indication, disease, and drug effects across adults and pediatrics, but it is unclear whether similar safety profiles for adults and pediatrics are required.

Additionally, the Agency has stated previously that extrapolation is not suitable for oncology indications. We request further clarification on this matter.

C. Ethical Considerations

Since Section IV. Ethical Considerations includes general principles for pediatric clinical studies, we suggest positioning this section prior to the sections on clinical pharmacology considerations (currently Section III) and the pediatric study plan design (currently Section IV).

BIO suggests that FDA expand upon the brief discussion of component analysis. While this discussion may be understandable to those with a background in ethics and are familiar with pediatric and literature, it may not be clear to clinical pharmacologists without such a background. It would also be helpful to include some references to deliberations of various commissions/committees regarding pediatric categories, prospect of direct benefit, minimal risk and minor increase over minimal risk, and component analysis, as many of these concepts will be new for many clinical pharmacologists.

Additionally, BIO believes that it would be helpful to include a brief discussion regarding the duration of treatment and how this might affect the prospect of direct benefit (*e.g.*, the limited benefit, if any, that might be expected from a single dose of study drug versus the prospect of direct benefit expected in a multi-dose study that lasts six weeks and includes an extension study to gather additional safety data).

Finally, we believe that it would be helpful to briefly discuss and enumerate the types of data that may be used to support the prospect of "direct benefit."

D. Pediatric Study Plans

To avoid redundancy, BIO suggests that Section V. Pediatric Study Plan Design and Points to Consider focus on three major areas: 1) development strategy including dose selection and labeling, 2) study design, and 3) data analysis. Additionally, it should be emphasized that



the approach for PK data analysis should be kept in mind when considering pediatric study design, age stratification, sample size, and PK sampling collection, as these factors are dependent on how the data will be analyzed and what PK parameter estimates are of importance for characterizing the drug PK over the various pediatric age populations.

The Draft Guidance indicated that pediatric study plans (PSPs) should be developed at an early development stage; however, the Draft Guidance did not provide much information with regard to the appropriate timing of the conduct of the pediatric studies (*e.g.*, concurrent with or after adult Phase 3 when sufficient safety and efficacy data are collected). General mention about the Agency's expectations for PSPs and the timing for the pediatric studies would be useful.

Additionally, the Agency should indicate clearly that it will allow both physiologically-based PK (PBPK) and population PK modeling together in a submission to support a pediatric application.

E. Age Groupings

The Draft Guidance provides two sets of age groupings (Lines 116-119 and 558). To prevent confusion, we suggest providing one set throughout the Guidance. The International Conference on Harmonisation *Clinical Investigation of Medicinal Products in the Pediatric Population E11* (ICH E11) provides an age classification currently in use by the European Medicines Agency (EMA), and we further suggest harmonizing the age classification in the Draft Guidance with ICH E11.

The Draft Guidance appears to suggest that weight or body weight dosing is needed, but lacks any direct commentary on this consideration. For example, there is no clear connection between the age groupings and the weight ranges provided (Line 485). Furthermore, weight or body weight dosing may not always be needed if, for example, a wide range of weights has already been studied in younger adults and no association between weight and clearance has been established. In such cases, fixed dosing, at least in older children, could be possible.

Most adult clinical studies exclude subjects younger than 18 years old; however, the Draft Guidance suggests that subjects from 16 to 18 years should not be represented in either pediatric or adult clinical research. We suggest that the Agency provides an additional category for subjects between 16 and 18 years, or consider changing the adolescent age group to 12 to 18 years.

As currently drafted, the Draft Guidance does not make a distinction between premature neonates and term neonates. BIO requests the Agency make a distinction between premature and term neonates and provide recommendations based on gestational ages. This clarity is important, since many maturation processes (*e.g.*, organs, enzymes) are more dependent on gestational age rather than date of birth, and the physiological differences between premature neonates and term neonates could impact dose selection.



F. Design for Pediatric Dose-Finding Studies of Oncology Drugs

Phase 1 pediatric dose-finding studies of oncology drugs require unique considerations, as the patient populations can be heterogeneous and difficult to access, and patients generally enter clinical trials following disease relapse after multiple standard of care and investigational treatments.

Practical constraints for the oncology therapeutic area should to be acknowledged and discussed in the Guidance and an oncology-specific case added in Section IV, given the unique considerations. In most cases, a broader age range of inclusion is applied to pediatric oncology Phase 1 studies than in other therapeutic areas. For example, age-stratified dose-finding may not be feasible in oncology studies, and the design of the pediatric Phase 1 dose escalation study across the relevant pediatric age range will need to be informed by considerations specific to the investigational agent (*e.g.*, predicted pediatric PK, therapeutic index expectations, nature and manageability of treatment-emergent toxicities, informed by prior adult information). In addition to the decision tree provided in the Appendix, we suggest including a guidance tree with an algorithm on modeling to assess the first dose and dose-finding for oncology studies.

Given the challenges of such, definitive understanding of age-PK relationships may only be possible retrospectively via population PK modeling after a sufficient amount of clinical data has been collected in Phase 1 and early Phase 2 pediatric studies. This caveat should be acknowledged, as it would not be clinically practical to conduct tiered pediatric Phase 1 studies in oncology patient populations where dose escalation is first performed in older children followed by younger children based on PK and safety data in the older age group.

Selection of dosing and age range should balance safety and overall benefit: risk with practical considerations for clinical studies in these populations. As noted above, Sponsors should be encouraged to maximize the value of prior information in adults to the extent possible via model-based strategies (*e.g.*, physiologically-based pharmacokinetic [PBPK], population PK modeling and simulation, and exposure-response understanding in adults) to drive designs of pediatric oncology Phase 1 studies in a manner that ensures patient safety and favorable benefit/risk while also addressing practical considerations associated with pediatric oncology clinical research. In such cases, modeling and simulation can be especially critical to define dosing in the pediatric phase 1 study in order to adequately minimize risk for specific age groups where developmental maturation and body size changes can be significant.

The Draft Guidance already makes reference to population PK in an efficacy trial providing concurrent confirmation of PK in the age subgroups (Lines 415-416). As this approach will likely be the approach in most oncology pediatric development plans, it will be useful to note this explicitly, given the unique challenges of oncology pediatric studies.



G. Sample Collection

Considering the limitations regarding the number of blood draws, amount of total blood volume that can be collected, etc., the Guidance should include the option for other creative ways to obtain blood/plasma for PK or PD analyses. For example, it is possible to use blood/plasma salvaged from samples taken for other purposes (*e.g.*, safety labs). Potential differences in derived PK parameters should be sufficiently scientifically documented and cross-validated when concentrations in whole blood, dried blood spots, or capillary blood are measured in the pediatric populations and compared to venous plasma concentrations in adult populations.

H. Internet Link to Physiological Data

In the future, accepted pediatric physiological information may change or more information may become available (*e.g.*, with respect to transporters). The references currently provided are useful, but we believe it would be useful to include links to the FDA website where the most recent accepted physiological data can be found. Additionally, providing general information in tabular format would be useful and easy to reference.

CONCLUSION:

BIO appreciates this opportunity to comment on the Draft Guidance for Industry entitled "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)



SPECIFIC COMMENTS

SECTION	COMMENT(S) WITH RATIONALE	PROPOSED CHANGE
II. BACKGROUND		
Line 59	"...Section 505 of the FD&C Act..."	"...Section 505 of the Federal Food, Drug and Cosmetic Act (FD&C) ..."
III. CLINICAL PHARMACOLOGY CONSIDERATIONS		
Lines 98-101	The Draft Guidance states "If there is a concern that exposure-response relationships might be different in pediatric patients, studies relating blood levels of drug to pertinent pharmacodynamics (PD) effects other than the desired clinical outcome (exposure-response data for both desired and undesired effects) for the drug in the pediatric population might also be important."	BIO requests that FDA clarify whether this portion of the Draft Guidance refers to one or more of the specific approaches, and explicitly state the approach/approaches being referred to.
Lines 98-100; 121-124	Current wording suggests that evaluation of the PD effects might be important when there is concern that exposure-response relationships might be different between adults and pediatric patients. However, the language in Lines 121-124 suggests that measurement of both PK and PD, along with a description of the exposure-response relationship, is essential in pediatrics.	BIO suggests that the Draft Guidance should distinguish cases where PK characterization alone is sufficient for exposure-response information from those where both PK and PD are necessary.
Lines 101-105	The Draft Guidance states "For all three approaches, the extent of the required pediatric safety studies may take into consideration prior experience with similar drugs in pediatric populations, the seriousness of the adverse events in adults or in pediatric populations, when this information is available, and the feasibility of conducting studies in pediatric patients."	BIO asks FDA to clarify whether the reference to pediatric safety studies is referring to long-term safety studies. Additionally, we recommend that FDA provide a similar summary of PK considerations from a development/age perspective.
Lines 108, 286-288	"Thus, for a clinical investigation to be approved by an IRB under this category, the enrolled pediatric subject must have a disorder or condition. A condition may	BIO asks the Agency to provide clarification on and examples of what the phrase "'at risk' for the disease" means (e.g., does this include genetic predisposition?)



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	include being 'at risk' for a disease."	
Lines 109-111	<p>"The identification of the appropriate ages to study and decisions on how to stratify data by age are drug-specific and require scientific justification, taking into consideration developmental biology and pharmacology."</p> <p>It is important to note that age is not always the most influential factor on PK. For some drugs, stratification by body size may be more relevant to dose finding in pediatrics. Additionally, stratification decisions may also be disease specific. For example, in pediatric oncology studies, stratification by age for safely studying older children before dosing in younger children is not realistic.</p>	BIO requests that the Draft Guidance be updated to reflect such cases where stratifying by age may not be realistic.
Lines 116-119; 558	These two sections of the Draft Guidance use two different age categories. Additionally, EMA uses different age categories for the pediatric groups in the ICH E11 guidance.	BIO recommends harmonizing the definition of pediatric age groups between FDA and EMA as well as using one set of age categories throughout the Guidance to prevent confusion.
Line 119	According to the age categories provided, 17 year olds are not considered adolescents.	BIO asks FDA to clarify the categorization of 17 year olds and whether they should be considered adults and not included in pediatric studies.
Lines 124-125	"In some instances, knowledge of pharmacogenetic differences, which can affect a product's exposure, may also be required."	BIO asks FDA to clarify how these pharmacogenetic differences manifest with regard to age and maturity.
<i>A. PHARMACOKINETICS</i>		
Lines 141-142	"Special areas of importance in planning pediatric PK studies are discussed in the following paragraphs."	BIO believes that it would be valuable to have a table summarizing the age/maturity differences for the various ADME factors, as well as known enzyme/transporter ontogeny.



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Lines 154-161	<p>This section of the Draft Guidance discusses drug or biologic distribution.</p> <p>Given their high specificity and affinity, biologics may be subject to target-related distribution. Different expression levels of receptors (<i>e.g.</i>, FcRn for IgGs) may result in PK discrepancies.</p>	
Lines 165-173	<p>This section of the Draft Guidance discusses the importance of drug metabolism and in vitro studies performed in drug development in planning pediatric PK studies</p>	<p>BIO asks FDA to provide additional information on PK/PD modeling approaches that can be used to address changes in drug enzyme/transporter activity that occurs with developmental/maturation changes.</p>
Lines 177-181	<p>This section of the Draft Guidance discusses drug excretion</p>	<p>BIO suggests including considerations for gender effects based on hormones.</p>
Lines 188-190	<p>"In vitro plasma protein binding studies can determine the extent of binding of the parent and the major active metabolite(s) and identify specific binding proteins, such as albumin and alpha-1 acid glycoprotein"</p>	<p>BIO requests additional information on how these in vitro studies compare with ex vivo studies.</p>
Lines 192-198	<p>This section of the Draft Guidance discusses clearance.</p> <p>For some biologics, the development of anti-drug antibodies (ADA) may result in reduced PK exposure.</p>	<p>BIO suggests including special considerations for biologics and immunogenicity, potentially under a separate subheading entitled "Immunogenicity" (also, see comment for Lines 200-207 below).</p>
Lines 200-207	<p>This section of the Draft Guidance discusses additional factors in planning pediatric PK studies.</p>	<p>BIO asks FDA to include a more detailed discussion of the important factors to consider when scaling clearance from the adult to the pediatric population and how the relative importance of these factors may vary with age (<i>e.g.</i>, body size in older children vs. body size and development/maturation changes in younger children). For neonates, it may be important to specify gestational age. We also suggest including BMI as a measure of body size.</p>



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		Additionally, BIO asks what pediatric considerations exist for immunogenicity evaluations, as immune systems are subject to a maturity process.
<i>C. PHARMACOGENETICS</i>		
Lines 226-235	This section discusses pharmacogenetics as having the potential to provide additional information in the interpretation of PK and PD results.	BIO recommends that the Draft Guidance use either “pharmacogenetic” or “pharmacogenomics,” but not both. If the use of both terms is intentional, we suggest defining the difference between “pharmacogenetic” and “pharmacogenomics.”
IV. ETHICAL CONSIDERATIONS		
Lines 261-262	“...or (2) in such a way that it offers the enrolled child a prospect of direct clinical benefit.”	BIO requests that the Agency clarify whether biomarker data alongside PK data will better support the “prospect of direct clinical benefit,” as target engagement can be realized.
Lines 269-271	“Consequently, healthy pediatrics subjects (<i>i.e.</i> , without a disorder or condition which is the focus of the research) cannot be enrolled in clinical pharmacology studies absent a determination by the Commissioner...”	BIO suggests editing the text to read: “Consequently, healthy pediatric subjects...cannot be enrolled in clinical pharmacology absent <u>without</u> a determination by the Commissioner...”
Lines 291-294	In programs that have a primary pediatric indication, the characterization of risk would likely be only with non-clinical data.	BIO requests clarifications if this requires the use juvenile animals.
Line 316-319	“This approach to the analysis of clinical pharmacology trials is called a component analysis of risk, whereby the interventions that do and do not offer a prospect of direct benefit in any given protocol must be analyzed separately.”	To allow the overall risk to be assessed, BIO believes that the entire protocol should be analyzed as a whole, rather than analyzing each component separately.
V. THE PEDIATRICS STUDY PLAN DESIGN AND POINTS TO CONSIDER		
<i>A. APPROACHES TO PEDIATRIC STUDIES</i>		
Line 366	Calling this approach a “PK Only Approach” can be misleading because safety trials are still required, as	We recommend renaming all three approaches



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	<p>shown in the decision tree.</p> <p>Additionally, in some instances described in the Dunne et al. paper (cited in Reference 27), it can be a safety-only approach.</p>	
Lines 370-375	<p>The Draft Guidance reads “Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions”</p>	<p>BIO suggests including editing the sentence as follows:</p> <p>“Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions, the same molecular target or pathway as the primary driver of disease pathophysiology in adults and pediatrics, and that inhibition of the molecular target/pathway is associated with effectiveness in adults in the disease under consideration.”</p> <p>This scenario is particularly relevant for molecularly targeted anticancer agents that target patients with tumors that are addicted to specific oncogenes, with associated signaling being inhibited by the drug. A classic example is Bcr-abl inhibitors for Ph⁺ CML.</p>
Lines 389-392	<p>“The disease and intervention are believed to behave similarly in pediatric patients and adults, but the exposure-response relationship in pediatric patients either inadequately defined or thought not to be sufficiently similar.”</p>	<p>BIO asks FDA to please clarify what type of evidence is required.</p>



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Lines 396-398	“Clinical measures (<i>e.g.</i> , symptoms, signs, outcomes) can be used to select doses, but an appropriate biomarker considered to be related to such an endpoint can also be used, which is usually a biomarker based on adult experience”	BIO asks FDA to specify the criteria for what is considered an “appropriate biomarker.”
Line 402	The provided antiarrhythmic example is a special case because it would be unethical to go with the “no extrapolation” option, leaving the Sponsor no choice but to take the “partial extrapolation” approach. The guidance would be more useful if it provided a different example where “partial extrapolation” is acceptable despite the feasibility of fully assessing efficacy through “no extrapolation” approach	BIO recommends that FDA give a different example of where partial extrapolation is acceptable.
Lines 415-416, 423	“A population PK analysis can be conducted concurrently using PK data from the efficacy study to confirm PK estimates in the age subgroups.”	BIO asks FDA to clarify whether a separate PK study is needed in the “PK and Efficacy (no extrapolation)” category, and if the Sponsor should plan to obtain population PK information from the efficacy study. Additionally, please consider cross-referencing with Line 686.
Lines 423-427	This paragraph appears to contradict previous text about the need to evaluate the drug over the entire pediatric age range in which it will be used.	BIO asks FDA to please clarify the need to evaluate the drug over the entire pediatric age range which it will be used.
<i>B. ALTERNATIVE APPROACHES</i>		
Lines 431-436	This paragraph provides a list of other approaches that can be used to obtain useful drug exposure information.	We suggest including dried blood spot (DBS) as an alternative approach, and cross-referencing to section V.F (Sample Collection)
Lines 438-446	This paragraph describes situations in which interpolation or extrapolation of PK data may be sufficient.	This paragraph would benefit from a more in-depth description of the techniques available (allometric scaling to allometric + maturation function to more sophisticated mechanism-based approaches) that help predict pediatric exposures and guide the starting dose in pediatric



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		studies by taking into account growth and development in the pediatric population
<i>C. PEDIATRIC DOSE SELECTION</i>		
Line 448	<p>“C. Pediatric Dose Selection”</p> <p>While existing clinical data are most important with regard to dose selection, nonclinical data may also provide useful information.</p> <p>Additionally, biologics, given high target specificity, typically have a wider therapeutic window, especially for subcutaneously-administered biologics. Although mg/kg may be used in initial PK studies, a fixed dose is preferred even within children within a certain weight range. For biologics in non-infants, body weight usually overshadows other PK covariates, including age.</p>	<p>BIO recommends that FDA provide additional examples in the text of the guidance and provide additional, relevant references.</p> <p>BIO also suggests FDA include a discussion on nonclinical data and pediatric dose selection.</p> <p>Finally, BIO believes that it is more appropriate to group pediatric patients by weight instead of age in dose selection studies.</p>
Lines 457-458	“Initial doses are typically normalized to body size (mg/kg), or BSA (mg/m ²).”	<p>BIO suggests editing the text to read:</p> <p>“Initial doses are typically normalized to body size (mg/kg), or BSA (mg/m²), or fixed doses stratified by body weight categories.”</p>
Lines 460-469	This paragraph only focuses on pediatric dose selection using the PK-only approach, rather than also providing considerations for the “no extrapolation” and “partial extrapolation” approaches.	BIO recommends providing additional considerations for the “no extrapolation” and “partial extrapolation” approaches
Lines 471-483	This paragraph discusses <i>in silico</i> and other alternative modeling approaches to provide preliminary data to inform study design	We recommend moving this paragraph to section V.B Alternative Approaches.
Line 485-486	It should be noted that weights in the disease state may differ markedly from growth charts based on healthy children	BIO asks FDA to consider adding a statement that growth charts may not be approximate actual weights in certain disease states (e.g., renal, liver, GI disease,



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		diabetes, cancer).
Lines 481-483	Additional guidance here is important because a purely bottom-up pediatric PBPK simulation without evaluation of the model's predictive ability to explain existing adult PK would not be appropriate.	<p>BIO suggests explicitly noting the following:</p> <p>"Ahead of performing PBPK model-based simulations of pediatric PK in different age groups to guide dosing and study design for the first-in-pediatric study, it is important to ensure that the model is qualified to be able to adequately describe the adult PK data and the sources of variability in adult PK."</p>
Lines 485-493	While this paragraph makes an important reference to the wide range of weights that are possible for a given age grouping, specific guidance on what to do about this is unclear.	BIO asks FDA to provide clarity and additional guidance on the range of weights for a given age grouping.
Lines 491-494	The Draft Guidance reads: "An estimate of the exposure-response relationship across a range of body size doses (mg/kg or mg/m ²) may be important. For the "PK and PD" and "PK and efficacy" approaches discussed in section V.A above, investigation of a range of doses and exposures should allow assessment of those relationships and development of rational dosing instructions."	<p>BIO suggests replacing this text with the following to ensure clarity:</p> <p>"The recommended posology (e.g., mg/kg, mg/m², binned dosing by age or body size categories) should be supported by understanding of the effects of factors like age, body size/weight on PK, and an assessment of the variability in achieved systemic exposures in the pediatric population in context of exposure-response relationships for PD or efficacy."</p> <p>Additionally, we suggest explicitly recommending that population PK methods are best suited for these evaluations</p>
<i>D. PEDIATRIC DOSE FORMULATION</i>		
Lines 508-510	There are times that the chemical properties of a molecule might make its formulation as a pediatric	BIO recommends amending the sentence as follows:



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	drug product technically unfeasible. In those cases, proper justification should be submitted by the sponsor and a waiver from this requirement should be granted.	“If there is a pediatric indication, an age-appropriate dosage formulation must be made available for pediatric patients if development of such a formulation is feasible. ”
Lines 513-516	“If the sponsor demonstrates that the reasonable attempts to develop a pediatric formulation have failed, the sponsor should develop and test an age-appropriate formulation that can be prepared by a pharmacist in a licensed pharmacy using an FDA-approved drug product and commercially available ingredients.”	BIO requests that FDA clarify the expectations of the Sponsor to provide compounding information to a pharmacist. We also request that the Agency provide further guidance with regard to ensuring compound stability in formulations prepared by a pharmacist, as poor solubility and sophisticated technologies used to enhance exposures in adult formulations may impact drug stability in various child-friendly matrices (<i>e.g.</i> , breast milk/formula, syrups, food).
Lines 521-523	<p>“A statement that the volume to be prepared is appropriate to be dispensed for a course of therapy for one patient, unless there are safety factors that necessitate decreasing the volume to be prepared”</p> <p>There are other safety issues that need to be considered. For example, if the formulation includes novel constituents, the safety of these may need to be established, as existing excipient databases provide safety for adults but not necessarily for children.</p>	BIO suggests that FDA include consideration of other pertinent, pediatric-specific safety issues.
<i>E. SAMPLE SIZE</i>		
Line 544	“E. Sample Size”	BIO believes it would be helpful for the Agency to provide additional examples in the text and/or additional relevant references.
Lines 546-547	“The precision of PK and exposure-response parameters in the sample size calculation is critical for pediatric studies.”	<p>BIO suggests editing the sentence as follows:</p> <p>“The precision of estimates of PK and exposure-response parameters in the sample size calculation is critical for</p>



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		pediatric studies."
Lines 549-551	<p>"The sponsor should account for all potential sources of variability, including inter-subject and intra-subject variability, and difference between the adult and pediatric populations in the final selection of the sample size for each age group."</p> <p>Does this imply that study enrollment should be stratified by age group?</p>	BIO recommends FDA considers stratification of the study sample based on ranges of body weight, rather than age, as an acceptable approach.
Lines 555-557	The Draft Guidance states the "pediatric study plan should specify whether premature or small for gestational age infants will be included in the study population."	BIO recommends that FDA clarifies the criteria that define "preterm infant" or "small for gestational age infant."
Lines 562-567	<p>It is unclear how 60% and 140% were selected as the boundaries for the recommended interval. The range is expected to be asymmetrical for the logarithmic mean; accordingly, the target confidence interval should be 60%-167%. It is also unclear whether this requirement applies to PK studies with intensive sampling or efficacy studies with sparse sampling. For PK studies with intensive sampling, we recommend to consider the precision of AUC or C_{max} measures instead of clearance and volume of distribution estimates.</p> <p>Additionally, although an accurate estimate drug exposures in pediatric patients across all ages is desired, the Agency should more openly discuss the advantages and disadvantages of noncompartmental versus population PK analysis of pediatric PK data.</p> <p>In the past, the Agency has rejected model-predicted</p>	<p>BIO suggests modifying the sentence as follows:</p> <p>"Justification for the sample size should be provided for the sample size selected. For example, one approach would be to prospectively target 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution in each pediatric subgroup with at least 80% power in terms of the precision of the estimates of one or two key parameters (e.g., AUC or C_{max})." </p>



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	<p>AUC estimates for labeling and asked specifically for AUC estimates using noncompartmental methods. In reality, it should be acknowledge that both noncompartmental and population PK methods are necessary to help inform the age groups with insufficient numbers of patients to reliably estimate clearance and volume of distribution parameters.</p> <p>When using the population PK approach and prospectively designed pediatric studies, bias, as well as precision, of the model-based PK parameter estimates (hence exposure predictions) should be taken into account for sample size determinations.</p>	
Lines 572	<p>"2. Number of Samples Per Patient"</p> <p>The Draft Guidance does not mention how to assess the samples per patient (as there is in the sample size section). Simulations may demonstrate tradeoffs between number of patients and the number of samples per patient. For example, a sponsor can sample at 10 time points from 10 patients (intensive sampling) or sample from 50 patients with peak and trough methods. Each group has 100 samples taken, so it is unclear what the relative value of either method to show similarity or difference to the adult kinetics.</p>	<p>BIO recommends including a more integrated discussion of sample size and samples per patient, reflecting that they are different levers to attain degree of certainty required, impact to the benefit/risk of patients, and ethical considerations of the study.</p>
Lines 579-580, 606-608	<p>"Additional sampling for drug or metabolic concentrations is also recommended when an adverse event occurs"</p> <p>"If possible, collect additional PK samples when adverse events are observed to understand the relationship between drug exposure and toxicity."</p>	<p>BIO notes that additional blood sample collection at the time of an adverse event may not always be scientifically appropriate to perform, as the temporal relationship between adverse event intensity and systemic concentration can be characterized by delays for various reasons depending on the specific adverse event of interest.</p>



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<i>F. SAMPLE COLLECTION</i>		
Lines 582-609	This section discusses sample collection in pediatric study plan design.	<p>BIO recommends that FDA provides additional guidance and/or reference documents regarding acceptable blood volumes that can be taken from children in specific time periods.</p> <p>Additionally, given the recent attention of microsampling techniques within industry, we ask FDA to highlight and provide additional guidance on dried blood spot analysis, since the pediatric population is ideally suited to this technique.</p>
Lines 596-597	"Sampling technique is critical when using the available pediatric indwelling intravenous catheters.	BIO asks FDA to clarify what critical sampling techniques are being referenced in these lines.
<i>G. COVARIATES AND PHENOTYPE DATA</i>		
Line 611	This section discusses covariates and phenotype data in pediatric study plan design.	We suggest the Agency address whether a drug-drug interactions study can be conducted in adults to support a combination therapy in pediatric patients
Lines 613-615	<p>"The sponsor should obtain the following covariates for each pediatric patient: age, body weight, BSA, gestational age and birthweight for neonates, race or ethnicity, sex, and relevant laboratory tests that reflect the function of the organs responsible for drug elimination."</p> <p>Lack of correlation between clearance and birthweight from adult PK data may be evidence that the birthweight-normalized dosing in pediatrics is not needed, at least in an initial PK study where it could be then confirmed.</p> <p>Dosing in the pediatric population may require a</p>	BIO requests comment on the use of PK analysis to extrapolate covariate findings from adults to pediatric population.



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	weight-based paradigm that is not the typical case with adult indications using small molecules. As biologics are weight-based, there could be an issue with the presentation in the parenteral form.	
Lines 616-618	"Sponsors are encouraged to collect DNA samples in pediatric PK studies under the circumstances described in section II..."	Typographical error, should reference Section III
Lines 639-641	Iohexol is used to measure, rather than estimate, glomerular filtration rate.	BIO suggests editing this sentence as follows: "In pediatric PK studies, an estimation of creatinine clearance is recommended because of the challenge with using exogenous markers such as iohexol as an estimate <u>to measure</u> of the glomerular filtration rate (GFR)."
Lines 644-645	"The Cockcroft-Gault formula should be used to estimate creatinine clearance in adolescents."	BIO suggests modifying this sentence as follows: "The Cockcroft-Gault formula should be used to estimate creatinine clearance in adolescents <u>and adults</u> ."
Line 650	The Draft Guidance provides the modified Schwartz equation.	Please provide a definition of pediatric patients for the modified Schwartz equation.
Lines 650-664	"Infant" was previously defined in this document (see Lines 116-119) as a subject from 1 month to 2 years, while "Neonate" was defined as birth to 1 month. In this equation, it seems that infant is defined as anything less than 1 year. This discrepancy in nomenclature can be confusing.	BIO asks FDA to clarify whether "neonate" is defined as birth to 1 month or less than 1 year and to use consistent terminology for clarity.
Line 658	"Infant (LBW < 1year): K=0.33"	BIO asks FDA to provide a definition of "LBW."
I. DATA ANALYSIS		
Line 691	"1. Noncompartmental Analysis"	BIO suggests including specific considerations for biologics, such as whether partial AUCs would be acceptable for biologics with long half-lives (e.g., IgG),



SECTION	COMMENT(S) WITH RATIONALE	PROPOSED CHANGE
		PD, and ADA.
Lines 712-713	It can be misleading to make a general statement that “sampling [for population PK analysis] can often be performed concurrently with clinically necessary blood sampling.” Clinically necessary blood sampling may occur once weekly, and in most cases, may not be sufficient to provide informative PK sampling for population PK analysis. This is very dependent on the drug's PK profile.	BIO suggests rephrasing to encourage as much concurrent PK and clinically necessary blood sampling as possible to minimize the number of additional blood draws for PK alone.
Line 720	“Simultaneous modeling across all patients...”	BIO suggests clarifying which patients to include in the meta-analysis across patient populations (<i>i.e.</i> , would this be adults, adolescents, and younger children age groups).
VI. APPENDIX		
Line 741:	It is unclear how the Agency will define and use the term “similar exposure,” as it should be based on inter-patient PK/PD variability as well as the systemic exposure relationship regarding safety and efficacy.	BIO suggests FDA define and provide examples or additional guidance on how “similar exposure” will be used.
Line 742:	The decision tree provided does not address modeling and simulation to inform the design of the clinical plan.	BIO suggests the algorithm provided address modeling and simulation approaches that could be used, where appropriate, at decision points on the tree.