April 1, 2019

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

Re: Docket No. FDA-2018-D-4524: S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on "S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines" (Draft Guideline or Guideline).

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

One area where the guideline is of particular relevance to BIO, and is thus appreciated, is in establishing both clarity and flexibility around the need and value of studies conducted in nonhuman primates. The language in Section 3.3 that acknowledges the limited value of dedicated studies in postweaning juvenile NHP is supported, as is the final paragraph in Section 4 which specifically addresses the situation of "pediatric first" clinical development in neonates.

SECTION 1

Some of the suggested datasets (i.e., clinical data, ePPND) that inform the nonclinical pediatric plan would not generally be available or well-characterized at the expected time of pediatric submission. As such, the guidance should be clear as to whether these data need to be completed earlier than otherwise expected (e.g., in parallel with phase 3 per S6).

There are several references to in vitro nonclinical investigations BIO looks forward to using in vitro methods wherever possible if they help to support the program.

BIO believes that commentary to address the necessity of repeating juvenile toxicity studies on a prodrug of an approved drug when there may or may not be existing adult toxicity data for the prodrug would be helpful. It is currently unclear whether there any particular concerns or strategies to be considered in those cases.

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Throughout the document, text refers to juvenile animal studies (JAS) conducted in support of pediatric clinical trials. BIO suggests ICH consider expanding this concept to reflect the intent that the JAS more generally supports the pediatric population being evaluated with regard to clinical indication. For example, clinical trials for chronic pediatric indications will necessarily be shorter than the anticipated clinical use, but JAS should be designed to detect potential toxicities resulting from years of drug administration. These studies inform wider use once the product is on the market and as such we ask that the guideline not be so specific to individual trials.

Throughout document, we suggest that the text refer to study periods as "dosing period" and "recovery period/post-dose period" instead of treatment and post-treatment/off-treatment periods.

SECTION 2

BIO believes that both the figure and accompanying text describing key weight of evidence (WoE) factors to be considered can be a very useful tool to have in the guideline. However, currently we note that the figure is not easily aligned with the text. The figure should be supportive of the narrative text in the guideline rather than confusing. We suggest that either the final version of the figure and text be aligned in its terminology or that the figure be deleted. For example, the factors on the left of the figure are not described in the narrative text using the same language or terminology and thus could be confusing. If these discrepancies can be solved, the figure can play an important and useful role in providing the more detailed information in an easily digestible manner.

BIO suggests adding the following additional factors to the figure and text:

- disease severity,
- route of administration (ROA), and
- assessment whether the ROA is affected by age.

BIO believes that text stating that the figure is for illustrative purposes and not a submission requirement would be helpful.

It is currently unclear to what extent feasibility (discussed in Section 2.3.5) is considered when there is a need to do a juvenile tox study on very young monkeys and it's not practical/possible/necessary to combine it with an ePPND study. We note that this topic is discussed in Section 4 and suggest this text cross-reference to the appropriate discussion.

SECTION 3

Animal test system selection should include consideration of whether pharmacologically relevant animal models of disease is/are available, and whether they have an appropriate clinical phenotype.

Sometimes it is not feasible to dose animals developmentally matched to the patient population of interest. For example, the Intracerebroventricular (ICV) route of administration is difficult in very young animals but is easier in young children due to their

larger size and access to highly specialized neurosurgeons. BIO suggests that the Guideline should state that age-matched animals are desired, when feasible.

Section 3.1, 'General Considerations/Study Objectives', of the S11 draft guidance "contains recommendations on study design considerations, core endpoints to be included in all studies, and additional endpoints that can be included to address specific concerns." However, based on the potential safety concerns related to individual products, targeted studies to address specific safety concerns may be more appropriate than general toxicity studies. Therefore, BIO recommends that the use of core endpoints should not be required in studies designed to address specific targeted safety questions.

CNS assessments are described in Section 3.8.2.6. Functional observational battery (FOB) and learning/memory maze assessments are commonly performed in rodent juvenile tox studies regardless of whether or not the drug has a CNS-specific effect. It would be helpful if this section could clearly describe whether this is necessary, or if the FOB and the mazes should only be performed if there is a CNS-related concern. We ask that the guidance clarify what is a CNS related concern and what is this based on.

SECTION 4

This section should be expanded to elaborate on why a nonclinical program with adult animals would be needed for an investigational drug targeted for pediatric only indication, unless adult animals are needed to support a first in human (FIH) study in healthy adults. Also, animal models could be discussed in this section as well; specifically to highlight that disease severity as the animal/person ages can be critical for identifying initiation and duration of treatment.

SECTION 5

We suggest the guideline discuss expectations for qualification of impurities specifically for pediatric populations.

Conclusion:

BIO appreciates this opportunity to comment on "S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines." Specific, detailed comments to the draft guideline

are included in the below chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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Emerging Companies Section & Senior Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization

/S/

Victoria A. Dohnal, RAC Senior Manager,
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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
1. INTRODUCTION		
1.1 Objectives of the Guideline		
Lines 24-26:	The Draft Guidance states "The purpose of this document is to recommend international standards for, and promote harmonisation of, the nonclinical safety studies recommended to support the development of paediatric medicines."	BIO notes that this statement implies a study is always required, which is not always the case. BIO suggests that for clarity the guideline be edited to indicate that the guideline should be consulted to determine the whether a study is warranted as part of a harmonized nonclinical safety assessment. As such, BIO suggests editing the text to read: "The purpose of this document is to recommend international standards for, and promote harmonisation of, the nonclinical safety assessment recommended to support the development of paediatric medicines."
Line 26:	The use of the term "paediatric medicines" implies the primary target population was paediatrics which is usually not the case.	BIO suggests editing the text to read: "… nonclinical safety studies recommended to support the development of ~~paediatric~~ medicines intended for pediatric use."
1.2 Background		
Lines 31-33:	The Draft Guideline states "Several regional guidelines have previously been issued by various regulatory agencies and were not in complete agreement on the need for, timing of, and design of juvenile animal studies (JAS)."	BIO notes that this sentence is incomplete. BIO suggests editing the guideline to indicate that as a result, this guideline has been drafted to harmonize discrepancies across regional guidelines and as such, supersedes these previous guidelines.

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Line 36:	The previous paragraph states there are some discrepancies across current ICH guidances regarding JAS. In addition to "complementing" these existing guidances, it should be stated that the intention of this guidance is to clarify and align any discrepancies.	BIO suggests editing the text to read: "…the current guideline is intended to complement and clarify the existing ICH guidelines."
1.3 Scope		
Lines 43-44:	It is stated that S9 should be consulted to provide clarity on the need for JAS for oncology agents. However, S9 is very ambiguous on this point. There would be great benefit for S11 to provide some clarity or examples on situations when such studies would be warranted.	
Lines 47-48:	The term "cellular therapies" is very broad. We suggest either providing some examples, or alternatively, it may be more helpful to state which modalities are in scope.	BIO suggests editing the text to read: Tissue engineered products, gene and cellular therapies, and vaccines are generally excluded from the scope of this guideline**,** but could be considered on a case-by-case basis.
Lines 47-48:	The Draft Guideline states "Tissue engineered products, gene and cellular therapies, and vaccines are excluded from the scope of this guideline."	BIO notes that peptides are not in scope of this guideline and asks that this be explicitly stated.
1.4 General Principles		
Lines 50-54:	The Draft Guideline discusses the rapid growth and development of organ systems within paediatric patient populations.	BIO notes that the rapid growth and development depends on what age is being referred to. Age 16-18 is pediatric, but comparable to 18+. Further, the temporal relationship of developmental processes and drug exposure (e.g. paediatrics exposed during the time of postnatal development while adults

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		exposed subsequent to development) is what's different between paediatrics and adults as opposed to the actual processes. BIO suggests the guideline be revised to read: "Paediatric patients, who will receive medicines during periods of rapid growth and postnatal development of several organ systems, may represent a population different from adults. Immaturity of organ systems in paediatric patients as well as maturation of systems during drug treatment can affect drug pharmacokinetics (PK), pharmacodynamics (PD), and/or off-target effects of medicines, potentially leading to differences in toxicity and/or efficacy profiles between paediatric and adult patients. ~~when considering the rapid growth and postnatal development of several organ systems.~~" Additionally, ICH E11 defines pediatric patients, a reference here would be helpful.
Lines 55-56:	The Draft Guideline states "An early consideration of nonclinical support for paediatric medicine development is recommended."	BIO notes that "early" is unclear. The initiation of JAS prior to proof-of-concept in clinical trials is unwarranted, unless the indication is "pediatric first".
Lines 59-61:	The Draft Guideline discusses the option to conduct Pre- and Postnatal Development (PPND) studies earlier than usual.	This suggestion is at odds with PIP or PSP requirements of conducting a pediatric study after demonstrating safety and efficacy in adults (Phase III trial)?

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Lines 60-61:	The Draft Guideline states "Another approach could be to conduct the Pre- and Postnatal Development (PPND) study earlier than usual."	BIO requests clarity around "earlier". We note that PPND studies are usually conducted in parallel with Phase 3 to support registration. Additionally, ICH S5 contains many potential additional endpoints that could be included in a PPND study. More specifics on what endpoints would be most relevant would be helpful. Also, a definition of "adequate exposure" would be helpful.
Lines 63-67:	This paragraph discusses making a weight of evidence based-decision to determine what nonclinical studies are needed. We note that this supports the objective of the guideline and should be moved earlier in the text.	BIO suggests moving this paragraph and integrating it into Section 1.1 of the guideline.
Line 69:	It would be helpful to provide examples when existing data would trigger the need for JAS.	BIO suggests adding a reference to the WoE examples in Appendix B.
2. DETERMINING THE NEED FOR ADDITIONAL NONCLINICAL SAFETY		
2.1 Clinical Context		
Lines 86-87:	The Draft Guideline states "This decision should be based upon a careful and cautious risk-benefit evaluation."	BIO believes that the use of "cautious" seems superfluous – "careful risk-benefit evaluation" would seem both scientifically robust and sufficient. As such, we suggest editing the text to read: "This decision should be based upon a careful ~~and cautious~~ risk-benefit evaluation."
Lines 87-89:	The Draft Guideline states "If a safety concern is identified for further clinical development, appropriate nonclinical studies (e.g., JAS) should be considered, and could be conducted in parallel with clinical investigation."	As currently written, it is unclear whether this refers to nonclinical findings. BIO suggests editing for clarity.

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		Additionally, it is unclear whether the clinical studies refer to adult and/or pediatric studies.
2.2 Weight of Evidence Approach		
Lines 91-94:	The Draft Guideline discusses the importance of an integrated assessment based on the totality of the evidence.	BIO suggests adding clarification that "clinical safety data" refers to adult clinical safety data.
Lines 99-101:	The Draft Guidance states "The WoE evaluation should be conducted when designing the initial paediatric development plan, but revisited if there are changes in age ranges and/or indications. The WoE outcome can be different for each trial depending on the paediatric population and the disease to be treated."	The information in these sentences seems somewhat redundant with statements made previously in lines 64-67.As such, BIO asks that clarification be made as to whether there is redundancy between the 2 sections noted, and revise accordingly.
Lines 99-101:	Pertinent new safety information should also be considered in the WoE evaluation.	BIO suggests editing the test to read: "The WoE evaluation should be conducted when designing the initial paediatric development plan, but revisited if there are changes in age ranges and/or indications or pertinent new clinical or nonclinical safety information."
Lines 107-108:	The Draft Guideline states "The list is not all inclusive for every situation, as there may be additional specific factors to consider (e.g., clinical management)."	BIO believes that "clinical management" is unclear and should be better defined in the guideline.
Lines 111-113 and 119-121:	There seems to be a conflict between these 2 statements where the text in the Figure 1 legend indicates that youngest patient age and known/suspected adverse effects on developing	

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	organ systems are the most important factors in determining the need for nonclinical studies, but the latter section indicates that the established efficacy and safety profile are the first point to consider.	
2.3 Factors to Inform the Weight of Evidence Evaluation		
Lines 124-125:	It is stated that nonclinical studies are likely warranted at the lower end of the age range. However, it is unclear whether this would still be true if there are no other triggers.	
Lines 126-128:	The Draft Guideline states "The duration of clinical treatment is another factor in determining whether additional nonclinical studies are warranted. Longer durations of treatment are more likely to expose a paediatric subject during a developmentally sensitive window."	It is unclear what "longer durations of treatment" means. BIO suggests including further discussion (e.g., 3 months, 6 months, chronic intermittent).
Lines 127-130:	The Draft Guidance states "Longer durations of treatment are more likely to expose a paediatric subject during a developmentally sensitive window. Whereas short-term use of a pharmaceutical is less likely to affect some aspects of development such as growth, a long duration of use is more likely to warrant further nonclinical studies than short-term treatments."	BIO notes that this is not necessarily true if short-term use happens to fall within the sensitive developmental window.
Lines 146-148:	The Draft Guideline states "If the known pharmacology of a medicine has the potential to impact the development of the intended paediatric population, or the role of the pharmacology on development is not understood or reasonably	If the pharmacological impact is known a study may not add additional value. BIO suggests clarifying the rationale for the benefit from a juvenile animal study may add to the pharmacologic safety profile in pediatrics.

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	predictable, further nonclinical investigations should be considered."	
Lines 153-156:	The Draft Guidance discusses the consideration of conducting in vitro or ex vivo investigations.	We believe this text is unclear and suggest editing to read: "In vitro or ex vivo investigations using juvenile (i.e., animal) or paediatric (i.e., human) tissues may be useful to determine potential age-related differences in sensitivity, density, and distribution of molecular pharmacological/toxicological targets." Also, practical feasibility for such investigation or to obtain paediatric tissues should be underlined.
Lines 166-169:	The Draft Guideline discusses PK modeling and simulation.	BIO suggests that the implications of PK modeling be included in the guideline. For example, the guideline should discuss alterations made to the pediatric clinical starting dose etc.
Lines 172-174:	The sentence states "Findings occurring in animals at similar exposures as those likely to be achieved in paediatric subjects are of higher concern…"	Is there a general exposure margin at which the level of concern would diminish?
Lines 175-176:	It is stated that safety signals in more than one species are of increased concern. This is not always the case if there is a (human relevant) biological rationale for why it was only observed in one species.	BIO suggests editing the text to read: "Safety signals that occur in adult animals of more than one species are more likely to be of increased concern."
Lines 176-178:	The Draft Guideline states "Depending on the age of the animals at study start and the endpoints	BIO believes it is currently unclear whether there is a concern for pediatric patients if adult toxicities did

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	included, some of these concerns may have been addressed in existing repeat-dose toxicity studies.	not translate to adult human studies and suggest a discussion on translatability be included. Additionally, we suggest revising the sentence to include developmental and reproductive toxicity (DART) studies besides repeat-dose toxicity studies: "…some of these concerns may have been addressed in existing repeat-dose or developmental and reproductive toxicity studies"
Lines 192-193:	The Draft Guideline states "These data in rodents are primarily relevant to preterm and term neonates if exposure is demonstrated."	BIO notes that some rodent systems mature postnatally vs. humans (e.g., myelination of CNS, metabolism) and suggest the sentence be clarified.
Lines 199-200:	There may be cases where the nonclinical toxicology data in adults has identified a hazard that is reasonably expected to be similar or worse in a juvenile such that additional JAS experiments to confirm this would not add value. A similar point is made in 2.3.2 "Further nonclinical studies might not add value when the underlying pharmacology has already identified a particular hazard." Addressing this in Section 2.3.4 is recommended.	BIO suggests editing the text to read: "…combination with data from the general toxicity studies in assessing the value of additional nonclinical investigations. There may be cases where the nonclinical toxicology data in adults has identified a hazard that is reasonably expected to be similar or worse in a juvenile such that additional JAS experiments to confirm this would not add value."
Lines 201-206:	A sponsor may also need to consider dose adjustments to account for changes in metabolism capacity.	We suggest this paragraph be edited to include this point.

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Lines 203-205:	BIO believes the statement "If a study in animals cannot be conducted with dose levels that provide acceptable systemic exposures in the range of those expected in paediatric patients..." implies that modelling would be needed (and acceptable) to determine the expected juvenile exposures relative to paediatric exposures.	We suggest clarifying how the assessment of predicted exposures in juvenile animals can be determined. A reference to Section 3.2 that describes DRF/PK studies may be appropriate.
2.4 Application and Outcome of the Weight of Evidence Evaluation		
3. DESIGN OF NONCLINICAL JUVENILE ANIMAL STUDIES		
3.1 General Considerations/Study Objectives		
Lines 217-221:	The first paragraph in Section 3 references – as part of Section 3 – to Section 3; this doesn't seem ideal as a section is referenced within itself.	BIO suggests moving this paragraph before the beginning of Section 3.
3.2 Preliminary/Dose Range Finding Studies		
Entire section:		BIO believes that this section is too directive, rather than allowing for flexibility in study design.
Lines 249-250:	The Draft Guideline states "In a preliminary or DRF JAS, lack of tolerability of a pharmaceutical at clinically relevant systemic exposures can indicate a significant concern for the corresponding clinical age range."	It is currently unclear whether this refers to adult clinically relevant exposures and how juvenile relevant doses are known if the pediatric clinical study has not been performed.
Lines 255-256:	The Draft Guideline states "In certain circumstances, DRF studies can explore the usefulness of particular endpoints, tissues, or biomarkers and thus refine the study design of the definitive JAS."	It is unclear whether the results of a DRF JAS study can be used to argue that a GLP study is not required. BIO believes this would be helpful.
3.3 Animal Test System Selection		

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Line 258:	It is stated that in most cases one species is sufficient.	BIO believes it would be helpful to provide an example where this is not the case.
Lines 260-261:	Pharmacological relevance should be a critical factor in choosing a nonclinical species. This is not explicitly mentioned here. On line 308, the phrase (non-relevant) is used and it is not clear if this refers to pharmacological relevance.	BIO suggests editing the text to read: "In all cases, the selected species should be justified, as nonclinical studies in a pharmacologically non-relevant species can give rise to misinterpretation and are not recommended."
3.4 Age of Animals, Dosing Period, and Dosing Regimen		
Lines 308-310:	We find the statement "In contrast to nonclinical studies for adult populations (see ICH M3), a short treatment duration in paediatric patients can require a longer dosing duration in the JAS to capture the developmental age range of the intended paediatric population." To be misleading since target organs could have been identified based on other studies (e.g., genotox, PPND) with demonstrated exposure.	
3.5 Off-Treatment Period Assessments		
Line 360:		We suggest adding "reproductive" to the sentence: "… (e.g., reproductive or behavioural assessment, immunological."
3.6 Route of Administration		
3.7 Dose Selection		
Line 393:	This section discusses "substantial changes in systemic exposure" but is not clearly defined.	BIO suggests providing a definition of "substantial changes in exposure.
3.8 Endpoints		

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Line 400:	This section discusses endpoints.	It is unclear whether all of these endpoints would also apply to an EPPND study. BIO asks for clarification of the scope of these endpoints.
Lines 422-424:		It is unclear whether sexual development should also be evaluated in case the off-treatment (recovery) period that encompasses the relevant developmental window (in rodents, to see any delayed effects if dosing limited to early ages (e.g., up to weaning).
Lines 429-435:	Only major organs are specified for histopathology, however organs that are undergoing development during the treatment period should be considered for histopathology.	BIO suggests editing the text to read: "Histopathology should be performed on major organs (e.g., those critical during development, such as bone, brain, ovary, testis, heart, kidney, liver) and those with macroscopic lesions."
Lines 429-435:	Testicular histopathology should include a qualitative evaluation of spermatogenic progression in mature animals. This is more than what is done in a standard adult toxicology study and the testis is already listed as a major organ to evaluate. This is well covered under section 3.8.2.7 as additional endpoints to address identified concerns which is more appropriate for this level of detailed evaluation.	BIO recommends either removing this sentence or moving it to section 3.8.2.7, "Testicular histopathology should include a qualitative evaluation of spermatogenic progression in mature animals."
Line 440:	Assessing toxicokinetics of major human metabolites should also be considered.	BIO suggests editing the text to read:

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		"…timepoints of sample collection. The TK assessment should consider both API and any relevant major human metabolites."
Lines 500-502:	We believe that it is unclear whether "Learning and memory should be evaluated typically during the off-treatment period as this period is most relevant to assess potential persistent or delayed effects." could also apply to all neurobehavioral testing.	Clarification on whether this is the case would be helpful.
Lines 542-543:		Sexual maturity is unlikely to be reached in NHP JAS, so please modify the sentence as follows: "In NHP, additional reproductive assessments are not ~~typically~~ included in JAS."
3.9 Allocation of Animals to Study Groups		
Lines 559-598:	This section discusses the allocation of animals to study groups.	BIO believes that this section is too specific for a guidance document and is overly prescriptive. As such we suggest deleting this section.
Lines 569-584:	There seems to be a contradiction between these 2 sentences in which litter sizes and sex ratios close to natural mean litter sizes is specified in line 569 but culling is mentioned in lines 584-586.	
3.10 Animal Numbers and Sex		
4. CONSIDERATIONS FOR PAEDIATRIC-FIRST/ONLY DEVELOPMENT		
	It is not clear that for pediatric first oncology indications, these should follow ICH S9 rather than ICH S11.	BIO suggests adding clarification on line 605 that pediatric first oncology indications should follow ICH S9.

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Lines 632-636:		It is unclear whether the use of surrogate molecules or genetically modified mice would be appropriate, as for adult testing.
5. OTHER CONSIDERATIONS		
Line 648:		It would be helpful to provide guidance as to whether impurity qualification data conducted in the course of adult nonclinical or clinical studies would be adequate for assessing paediatric safety.
5.1 Excipients		
5.2 Combination Pharmaceuticals		
GLOSSARY		
Line 673:		It would help to define PPND (rodents) vs ePPND (NHP).
NOTES		
Lines 700-702:	It is unclear whether this note means that immature organs examined (histology) at the end of dosing should also be examined when/if being mature at the end of the recovery period even if no findings were detected at the end of the dosing period (e.g., testis).	
REFERENCES		
APPENDIX A: OVERVIEW OF AGE-DEPENDENT DEVELOPMENT OF ORGAN SYSTEMS BY SPECIES		
Line 767:	Figure A6 is redundant and difficult to interpret. Figures A1 and A2 are more readily compared to provide the same information.	BIO suggests deleting Figure A6.
Line 771:	For Rat and Mouse, microsampling could alleviate potential concerns about sample size, dedicated	BIO suggests including the use of microsampling where possible.

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	cohorts of pups, and terminal collection necessary for conventional sampling.	
Table A1, page 31	The Guideline lists the following as a disadvantage for NHPs: "Offspring highly dependent on maternal care over first month (minimal procedural intervention recommended; pre-weaning manipulation & dosing feasible with risk of maternal rejection), and are cohoused with dam for first 3-6 months; with shipping and quarantine requirements it is rarely feasible to initiate studies in juvenile monkeys < 9 months of age"	BIO suggests editing the text to read: Offspring highly dependent on maternal care over first month (~~minimal~~ limited procedural intervention recommended, although pre-weaning manipulation & dosing feasible with experienced laboratories). Infant NHP are cohoused with dam for first 3-6 months; with shipping and quarantine requirements, it is rarely feasible to initiate studies in juvenile monkeys < 9 months of age in facilities that do not breed on-site
APPENDIX B: CASE STUDIES APPLYING THE WEIGHT OF EVIDENCE APPROACH		
APPENDIX C: EXAMPLE OF AN APPROACH TO RODENT PREWEANING LITTER ALLOCATION		
	BIO believes that Appendix 6 is too prescriptive.	We suggest deleting from the Guideline.