Biotechnology Industry Organization

September 13, 2013

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

Re: Docket No. FDA–2013–D–0814: Draft Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans; Availability

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans." BIO commends FDA on the release of this Draft Guidance and shares the Agency's commitment to ensure that safe and effective medicines are available for children.

BIO represents more than 1,100 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

A. Comprehensive Approach to Pediatric Drug Development

BIO strongly supports a comprehensive approach to pediatric drug development crafted in the best interests of children and greatly appreciates recent public comments made by FDA leadership championing this approach.

Recognizing that drug development is typically planned across multiple indications over many years and is dependent upon complex factors that ultimately determine the feasibility of studies in distinct populations across these indications, the Pediatric Research Equity Act (PREA) limited required pediatric studies to the adult indication under investigation. FDA should, therefore, continue to be clear about what is *required* in the Pediatric Study Plan (PSP) under PREA, as amended by the Food & Drug Administration Safety and Innovation Act (FDASIA).

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BIO believes, however, that these statutory obligations do not preclude the Agency from embracing a more comprehensive approach to pediatric drug development. BIO recommends that FDA:

(1) Allow Sponsors the *option* to include, in addition to the required components of the PSP under PREA, information needed to support discussion of additional, potentially beneficial, yet non-obligatory, pediatric uses of a product under the Best Pharmaceuticals for Children Act (BPCA),

(2) Reward this *optional* disclosure by agreeing to review and provide comments on these additional, non-binding proposals as they may apply to the Sponsor's future Proposed Pediatric Study Requests (PPSRs) and, ultimately, issuance of Written Requests for Exclusivity, and

(3) Clarify that any changes to these *optional* studies included in the initial PSP will not require an amendment to an agreed-upon initial PSP.

BIO strongly believes this *optional*, earlier dialogue on a comprehensive pediatric drug development plan, including both required research under PREA and potential pediatric uses under BPCA, will result in a more efficient pediatric drug development process. Please see the attached table of specific comments for suggested edits of, and insertions to, the text of the draft guidance to facilitate this approach.

B. Review Timelines for Initial and Amended PSPs and Communication Regarding Requests for Waivers/Deferrals

The deadlines by which the Sponsor should submit a PSP are given in Section IV, but the timeline for PSP review is not outlined in the draft guidance. BIO believes that including the timelines for the PSP process outlined in Section 506 of FDASIA and the current *Pediatric and Maternal Health Staff (PMHS) Standard Operating Procedure (SOP) for Review of Pediatric Study Plans (PSPs) and Written Requests by the Pediatric Review Committee (PeRC)* would provide greater clarity to the draft guidance. BIO also requests that FDA clarify whether the full review process (*i.e.*, 210 days) should be expected for amendments to the PSP and whether the PSP can be amended prior to submission or during review of a Biologics License Application/New Drug Application (BLA/NDA) or applicable supplemental application, if the information to be updated is unrelated to the application being submitted (*i.e.*, to clarify commitment dates or potential changes to deferred studies due to enrollment or retention issues, design issues, *etc.*).

While BIO welcomes earlier, more formal agreement on Pediatric Study Plans, there is still a disconnect between the timing of FDA's agreement on a PSP and, where applicable, final waiver/deferral decisions. BIO believes that, at a minimum, it would be useful for Sponsors to receive a recommendation as to whether their requests meet the standards specified in Section 505B(a)(3) and 505B(a)(4) of the Food, Drug, and Cosmetic Act.

If this issue is not addressed, earlier PSP agreements may not ultimately translate into earlier or more efficient pediatric drug development. If final waiver/deferral decisions are not made until the time of approval, FDA should describe (1) the circumstances under which changes to an agreed-upon initial PSP, with respect to waivers/deferrals, will be made; (2) how and when they will be communicated to the applicant, noting that the earlier in the review process the better for Sponsors; and (3) how these changes could affect approval of the application.

Furthermore, in order for comprehensive planning (discussed above) to facilitate more efficient pediatric drug development, it will also be imperative for Written Requests for Exclusivity to be issued in a timely manner in response to Sponsors' Proposed Pediatric Study Requests (PPSRs).

C. Nonclinical Studies in Juvenile Animals

To provide a unified approach to assessing the safety of therapeutics for pediatric populations, the need for nonclinical studies in juvenile animals should be aligned with, and reference, established guidance for nonclinical safety studies, as follows:

- ICH M3 (R2): *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*
    - Section 12: *Clinical Trials in Pediatric Populations*

- ICH S9: *Nonclinical Evaluation for Anticancer Pharmaceuticals*
    - Section 3.6: *Nonclinical Studies to Support Trials in Pediatric Populations*

The aforementioned International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance documents require an integrated assessment of the totality of the data (*e.g.*, drug target, completed nonclinical and clinical study results, patient population, disease indication, and the strengths/limitations of existing nonclinical models available) to evaluate safety concerns unique to pediatric patients and determine the questions that could be appropriately addressed by juvenile toxicity studies. This approach is essential to providing the most thorough scientific assessment of safety for pediatric patients, as well as maintaining Agency and Sponsor commitments to the 3Rs of Animal Testing (Reduce, Refine, Replace)[1], which aim to eliminate unwarranted animal studies.

Alignment with ICH M3 (R2) and ICH S9 also provides consistency with EMA/CHMP/SWP/169215/2005: *Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Populations*. That guidance also relies

[1] FDA Guidance for Industry: S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (2012), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf

on an evaluation of the totality of the available data against the unique considerations of the pediatric population under consideration to determine whether additional toxicity studies will provide clinically meaningful data. Compliance with these established guidance documents will more effectively support global drug development.

D. Global Pediatric Development

BIO recommends that FDA and the European Medicines Agency (EMA) work collaboratively to harmonize their regional programs in order to promote more efficient pediatric drug development. BIO has been engaged in, and supportive of, the development of many aspects of the current FDA pediatrics program and looks forward to the opportunity to provide input on the development of any harmonized documents and procedures at the appropriate time. Recognizing, though, that harmonization will be a lengthy and complex process, BIO does not believe efforts to achieve harmonization should delay the finalization of this draft guidance.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans." 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 W. Womack, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 26-34:	Footnote 3 is the only reference in the guidance where Sponsors are encouraged to consult directly with Pediatric and Maternal Health Staff (PMHS) in addition to review divisions.	BIO requests that FDA amend the text by moving footnote 3 into the body of paragraph and revising to read: "…Safety and Innovation Act (FDASIA).[2] In addition to consulting guidance, Sponsors are encouraged to contact the specific CDER/CBER review division ~~or~~ and the Pediatric and Maternal Health Staff to discuss specific issues that arise during preparation of the initial PSP."
II. BACKGROUND		
Lines 164-166:	It is unclear whether the page limit for the summary of the mechanisms of action applies to each Active Pharmaceutical Ingredient (API) or the sum of the APIs in fixed dose combination products comprised of more than one API.	BIO requests that FDA clarify whether, in cases of fixed dose combination products comprised of more than one Active Pharmaceutical Ingredient (API), the 1-5 page limit for the summary of the mechanisms of action applies to each API or the sum of the APIs in the drug product.
III. APPLICATIONS THAT REQUIRE SUBMISSION OF AN INITIAL PSP		
Lines 98-100:	It is unclear whether applications for new drugs or biologics initially developed for use in pediatric populations would require a PSP.	BIO requests FDA clarify that applications for new drugs or biologics initially developed for use in pediatric populations do not require a PSP.
Lines 98-100:	BIO believes that if previous pediatric studies have been conducted with a particular active moiety in a particular indication, the clinical information needed to describe the use of that treatment in children has been established.	BIO encourages FDA to use regulatory discretion when requiring PSP submissions and additional pediatric studies for new dosage forms, new dosing regimens, or new routes of administration. BIO encourages the use of Modeling and Simulation and/or extrapolation for additional information that may be needed when PREA is triggered with the same active moiety.

SECTION	ISSUE	PROPOSED CHANGE
Line 100:	Orphan-designated indications are generally exempt from PREA, and BIO believes this should be reflected in the guidance document.	BIO requests that FDA revise the text to read: "…route of administration (*i.e.*, that triggers PREA) is required to submit an initial PSP unless otherwise exempt from this requirement under 21 CFR 601.27(d), exemption for Orphan drugs.[15]"
IV. TIMING OF A PSP SUBMISSION		
Lines 111-112:	It is not clear what is meant by "required assessments."	BIO requests that FDA move reference 31 to this section, in order to clarify the definition of "required assessments" in this context.
Lines 111-126:	Orphan-designated indications are generally exempt from PREA, and BIO believes this should be reflected in the guidance document.	BIO recommends that FDA clarify that Orphan-designated indications are generally exempt from PREA and thereby do not require a PSP (noted above in comment on Line 100). BIO also recommends that FDA defer the requirement for a PSP when Orphan designation review is pending at the time of end-of-phase 2 (EOP 2) meeting until a decision has been issued by the Office of Orphan Drugs.
Lines 112-115:	Since it is stated in Appendix 1, Lines 385-386 that review and agreement may require at least 7 months, it is unclear whether Sponsors must wait for feedback before initiating any phase 3 study.	BIO requests FDA clarify that Sponsors need not wait for feedback before initiating any phase 3 study on any population.
Lines 118-120:	The procedure is unclear for obtaining scientific advice on the proposed PSP when there is no active Investigational New Drug (IND) Application for the drug and, upon submission of the IND, the initial studies would not include a phase 3 study.	BIO requests that FDA clarify the procedure for obtaining scientific advice on the proposed PSP when there is no active Investigational New Drug (IND) Application for the drug and, upon submission of the IND, the initial studies would not include a phase 3 study.
V. CONTENTS OF THE INITIAL PSP		

SECTION	ISSUE	PROPOSED CHANGE
Line 150:	BIO strongly supports a comprehensive approach to pediatric drug development and believes that Sponsors should have the *option* to include information needed to support discussion of additional, potentially beneficial, yet non-obligatory, pediatric uses of a product under the Best Pharmaceuticals for Children Act (BPCA) and should receive comments from FDA on these additional, nonbinding proposals as they may apply to the Sponsor's future Proposed Pediatric Study Requests (PPSRs) and, ultimately, issuance of Written Requests for Exclusivity.	BIO requests that FDA revise the text to read: "…discussed in section VI., Contents of Requested Amendment to an Initial PSP. While not a *required* component of the PSP by statute, Sponsors are encouraged to include information in the PSP to support plans for submission of a future proposed pediatric study request. Therefore, in addition to the required components of the PSP under PREA, this draft guidance also addresses the optional information needed to discuss additional potentially beneficial pediatric uses of a product. If a Sponsor chooses to include the optional information, FDA will review and provide comments on the additional uses of the product as it may apply to the Sponsor's future proposed pediatric study request and ultimately issuance of a Written Request for Exclusivity. This earlier dialogue on a comprehensive pediatric development plan (including both required research as well as potential pediatric uses under BPCA) is intended to result in a more efficient pediatric drug development process."
1. OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION		
Lines 154-160:	The purpose of this section is to establish the level of unmet medical need in pediatrics. BIO believes this should be stated much more explicitly to ensure consistency across FDA guidelines.	BIO recommends that FDA revise the text to read: "…methods of diagnosis, and currently available ~~treatments~~ therapy (as defined in FDA guidance) and/or prevention…" BIO also requests that FDA provide clear guidance on what is expected for the provision of incidence and prevalence of the disease in the overall population and the incidence and prevalence in the pediatric population information, in particular, with respect to rare diseases.

SECTION	ISSUE	PROPOSED CHANGE
2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT		
Lines 162-171:	BIO strongly supports a comprehensive approach to pediatric drug development and believes that Sponsors should have the *option* to include information needed to support discussion of additional, potentially beneficial, yet non-obligatory, pediatric uses of a product.	BIO requests that FDA revise the text to read: "This section should briefly summarize (1 to 5 pages) the proposed mechanism of action of the drug (to the extent understood) ~~and describe the potential therapeutic benefits or fulfillment of therapeutic needs in the pediatric population, including neonates~~. A broad consideration of any possible therapeutic uses of the drug in children beyond the disease or indication being sought in adults may serve as the basis for a Written Request under section 505A of the FDC&C Act (21 U.S.C. 355a). If a sponsor plans to submit a proposed pediatric study request asking the FDA to issue a Written Request in the future, a description of the potential therapeutic benefits or fulfillment of therapeutic needs in the pediatric population, including neonates, may ~~should~~ be included in the overview as appropriate.[23]"
3. OVERVIEW OF PLANNED EXTRAPOLATION TO SPECIFIC PEDIATRIC POPULATIONS		
Lines 173-197:	BIO welcomes the inclusion of information on extrapolation and Modeling and Simulation but believes additional clarity is needed regarding the types of approaches that are acceptable.	BIO requests that FDA provide additional clarity regarding the types of approaches that are acceptable for extrapolation and Modeling and Simulation, including potential extrapolation of safety data.
4. REQUEST FOR DRUG-SPECIFIC WAIVER(S)		
Lines 201-207:	It is unclear whether indicating the intent to request waiver(s) in the PSP negates the need to file a formal request, as outlined in the draft guidance on *How to*	BIO recommends that FDA revise the text to read: "…supportive information. If a Sponsor intends to submit a full or partial waiver request and has not done so prior to

SECTION	ISSUE	PROPOSED CHANGE
	Comply With the Pediatric Research Equity Act.[2] BIO believes, given the information needed in this section of the PSP is very similar if not the same as what needs to be submitted in a waiver request, that submission of information to support a partial or full waiver request in the PSP should serve as the official waiver request.	filing the initial PSP, then submission of information to support a partial or full waiver request in the PSP will be the official waiver request. It should be noted…"
Lines 201-212:	For a full waiver request the current guidance requires an extensive assessment. By contrast, the previous Draft Guidance for Industry on *How to Comply With the Pediatric Research Equity Act* required a checklist approach.	BIO encourages FDA to continue to make full disease waivers an option and to allow use by Sponsors of the previous checklist approach outlined in the Draft Guidance for Industry on *How to Comply With the Pediatric Research Equity Act*.
Lines 207-208:	BIO believes that when there is sufficient evidence for the Agency to grant a Waiver (*i.e.*, available data supporting a lack of efficacy or a substantial risk related to safety across pediatric age groups), the formal Waiver should be granted at the time of the initial 210-day review cycle.	BIO requests that FDA make this guidance consistent with draft guidance on *How to Comply With the Pediatric Research Equity Act* by revising the sentence to read: "...supportive information. ~~It should be noted that requested waivers in the PSP will not be formally granted or denied until the application is approved.~~[27] Waivers granted early in the pre-approval development period (*e.g.*, end-of-phase 1 or end-of-phase 2 meetings) reflect the Agency's best judgment at that time. If, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision. If this occurs, the PSP should be amended to

[2] FDA Guidance for Industry on How to Comply with the Pediatric Research Equity Act (2005), http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

SECTION	ISSUE	PROPOSED CHANGE
		reflect the FDA's new thinking (See Section VI). A waiver decision becomes final once issued in the approval letter for an NDA, BLA, or supplement.[27]"
5. SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES		
Lines 216-217:	BIO believes that "nonclinical studies" comprise more studies than the scope of this request.	BIO suggests that FDA consider revising the text to read: "…all planned: (1) relevant nonclinical studies that support the use of the drug in all pediatric age groups (if existing…"
Lines 218-221:	Additional data are used to support the design and initiation of pediatric studies, including modeling and simulation approaches.	BIO recommends that FDA revise the text to read: "…after the application is approved). This section also can include available data in adult or pediatric patients who have received treatment with the drug (or related drugs) for the proposed indication (or for other conditions) in earlier studies or a brief summary of the modeling and simulation approaches that will be used for study design and appropriate pediatric dose selection. A sample table…"
6. PEDIATRIC FORMULATION DEVELOPMENT		
Line 231:	BIO believes that "Pediatric Formulation Development" is too narrow a title for this section, and it should be renamed "Age-Appropriate Product Development" to more accurately reflect the scope of the section.	BIO recommends that FDA revise the text to read: "6. ~~Pediatric Formulation Development~~ Age-Appropriate Product Development"
Lines 237-240:	BIO believes that the reference to capsules and tablets is too narrowly focused; rather, FDA should include a sentence that Sponsors should "ensure appropriate design of a pediatric product," including mention of the requirement to possibly design different devices to meet pediatric	BIO recommends that FDA revise the text to read: "…pediatric formulation. Sponsors also should provide details ~~about the size of all planned capsules or tablets~~ of measures taken to ensure appropriate design of a product, including to the extent practicable the design of delivery systems (*i.e.*, capsules, tablets, devices, etc.), to be used

SECTION	ISSUE	PROPOSED CHANGE
	needs.	in pediatric studies.[29]"
7. NONCLINICAL STUDIES		
Lines 246:	BIO believes that ICH guidances pertaining to the types of preclinical studies relevant to predicting safety in pediatric populations should be referenced.	BIO requests that FDA revise the text to read: "…proposed clinical trials. When selecting appropriate nonclinical studies, Sponsors should adhere to appropriate international guidances for life-threatening indications such as advanced cancers (*ICH S9 Nonclinical evaluation for anticancer pharmaceuticals)* and other indications *(ICH M3 [R2] Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals).* The [S]ponsor should…"
Lines 250-257:	BIO believes that pharmacology, route of administration, and dosing frequency should be added to the list of data used to support clinical trials.	BIO recommends that FDA revise the text to read: " …endpoints to be evaluated • pharmacology • route of administration • dosing frequency"
9. PLANNED PEDIATRIC CLINICAL STUDIES		
9.1 PEDIATRIC PHARMACOKINETIC STUDIES		
Lines 270-286:	BIO believes that demonstration of pharmacokinetics (PK) in a pediatric population that is similar to adult PK can allow for the extrapolation of adult efficacy data to the pediatric population in circumstances where the disease course is well understood and similar between adult and pediatric populations.	BIO recommends that FDA include the principle that demonstration of PK in a pediatric population that is similar to adult PK can allow for the extrapolation of adult efficacy data to the pediatric population in circumstances where the disease course is well understood and similar between adult and pediatric populations.

SECTION	ISSUE	PROPOSED CHANGE
Line 287:	Due to the challenges in recruiting subjects for pediatric studies, the paucity of available patients due to the orphan status of most disease indications, and the fact that multiple sponsors for drugs in the same class all compete for the small pool of patients, feasibility should be addressed in this section.	BIO recommends that FDA revise the text to read: " • Sample size justification • Feasibility of planned pediatric clinical pharmacokinetic studies"
9.2 CLINICAL EFFECTIVENESS AND SAFETY STUDIES		
Line 297:	At the time of the initial PSP, BIO believes it is likely that only ***key*** inclusion and exclusion criteria could be defined.	BIO recommends that FDA revise the text to read: " • ~~Inclusion~~ Key inclusion and exclusion criteria for the study."
Line 303:	Due to the challenges in recruiting subjects for pediatric studies, the paucity of available patients due to the orphan status of most disease indications, and the fact that multiple sponsors for drugs in the same class all compete for the small pool of patients, feasibility should be addressed in this section.	BIO recommends that FDA revise the text to read: " • Statistical approach (e.g., statement of null and alternative hypotheses, sample size/power justification) • Feasibility of planned pediatric clinical effectiveness and safety studies"
11. PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES		
Lines 329-347:	It is unclear whether indicating the intent to request full or partial deferral(s) in the PSP negates the need to file a formal request, as outlined in the draft guidance on *How to Comply With the Pediatric Research Equity Act*. BIO believes, given the information needed in this section of the PSP is very similar if not the same as what needs to be submitted in a deferral	BIO recommends that FDA revise the text to read: "…currently available evidence justifying the request for a deferral (1 to 2 pages). If a Sponsor intends to submit a full or partial deferral request and has not done so prior to filing the initial PSP, then submission of information to support a partial or full deferral request in the PSP will be the official deferral request. It should be noted…"

SECTION	ISSUE	PROPOSED CHANGE
	request, that submission of information to support a partial or full deferral request in the PSP should serve as the official deferral request.	
Lines 347-349:	The draft guidance on *How to Comply with the Pediatric Research Equity Act* notes that decisions on deferrals can be made by FDA early in the pre-approval development period and in these cases, it is possible that FDA may re-evaluate the length of the deferral closer to the time of approval, taking into account any new information obtained while the product was in development and information reviewed in the NDA or BLA	BIO recommends that FDA revise the text to read: "…currently available evidence justifying the request for a deferral (1 to 2 pages). ~~It should be noted that requested deferrals in the initial PSP will not be formally granted or denied until the drug is approved.~~[34] Decisions on deferrals can be made by FDA early in the pre-approval development period and in these cases, it is possible that FDA may reevaluate the length of the deferral closer to the time of approval, taking into account any new information obtained while the product was in development and information reviewed in the NDA or BLA. Any relevant changes to a deferral would need to be captured in an amended PSP (See Section VI).[34]"
12. AGREEMENTS FOR OTHER PEDIATRIC STUDIES		
Line 359:	BIO strongly supports a comprehensive approach to pediatric drug development and believes that Sponsors should have the *option* to include information needed to support discussion of additional, potentially beneficial, yet non-obligatory, pediatric uses of a product under the Best Pharmaceuticals for Children Act (BPCA) and should receive comments from FDA on these additional, nonbinding proposals as they may apply to the Sponsor's future Proposed Pediatric Study Requests	BIO requests that FDA insert the following text at line 359: "**13. Additional information, if applicable, to support a proposed pediatric study request** If a Sponsor chooses to include information regarding the possible therapeutic uses of the drug in children, beyond the disease or indication being sought in adults to serve as the basis for a Written Request, the information can be detailed in this optional Section. If included, this section should provide a discussion of the additional work needed to support the potential beneficial therapeutic uses described in section 2 of the PSP, including an overview of

SECTION	ISSUE	PROPOSED CHANGE
	(PPSRs) and, ultimately, issuance of Written Requests for Exclusivity.	the disease(s) in the pediatric population, any planned extrapolation (with justification) for the new uses, additional formulation development that may be required, additional nonclinical studies that may be required, as much detail as available for additional clinical studies proposed to be conducted (PK, safety and effectiveness).”
VI. CONTENTS OF REQUESTED AMENDMENT TO AN INITIAL PSP		
Lines 361-372:	BIO believes it is unclear what constitutes an amendment that would require the submission of a PSP versus an amendment that would only require a submission of a protocol amendment to the IND for an abbreviated version of the 210-day process.	BIO recommends that FDA clarify what constitutes an amendment that would require the submission of a PSP versus an amendment that would only require a submission of a protocol amendment to the IND for an abbreviated version of the 210-day process.
Lines 361-372:	BIO believes it would be beneficial for Sponsors to have a clear outline of the process for approval of amendments to an initial PSP, as well as clear procedural guidance to assist Sponsors in resolving any disputed comments prior to submission of the Agreed Upon PSP	BIO requests that FDA include an outline of the process for approval of amendments to an initial PSP and clarify procedures to assist Sponsors in resolving any disputed comments prior to submission of the Agreed Upon PSP. In the case that an agreement is not reached at the end of the 210-day review period, BIO encourages FDA to consider a PDUFA Type A meeting to help reach agreement for a PSP.