September 12, 2013

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


Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit feedback in response to the Food and Drug Administration (FDA) request for comments on a draft guidance for industry entitled “Pediatric Study Plans [(PSPs)]: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.”

PhRMA is a voluntary, nonprofit association of the country’s leading pharmaceutical research and biotechnology companies, which are dedicated to inventing medicines that allow patients to live longer, healthier, and more productive lives. In 2012 alone, PhRMA members invested approximately $50 billion in discovering and developing new medicines, representing the vast majority of private investment in new biopharmaceutical products in the United States.

PhRMA shares FDA’s goal of ensuring adequate testing of drug and biological products in children. In fact, PhRMA strongly supported passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) that permanently reauthorized both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Permanent reauthorization of BPCA and PREA will improve medical care for children by driving research to create innovative medicines for use in pediatric patients. Additionally, permanent reauthorization of BPCA and PREA will create a more predictable and efficient pediatric drug development process and allow biopharmaceutical companies to continue to make significant investments in pediatric drug research. Further, PhRMA supports FDA efforts to assist sponsors in the submission of an initial PSP as required under FDASIA and commends FDA for providing straightforward and concise guidance detailing content and processes for

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2 Public Law 112-144, July 9, 2012.
3 See Section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as amended by Section 506 of FDASIA (Public Law 112-144, July 9, 2012).
PSPs intended to facilitate and expedite development and review of new drugs and biologics for pediatric populations. PhRMA looks forward to working with FDA and all stakeholders on issues related to pediatric drug development and the successful implementation of FDASIA for pediatric patients. Therefore, PhRMA appreciates the opportunity to provide the following comments to FDA on this draft guidance on PSPs.

I. SPECIFIC COMMENTS

A. Introduction: Comment on Reference to Contacting Specific Review Division and the Pediatric and Maternal Health Staff

PhRMA believes there needs to be greater clarity around both interactions between FDA review divisions and the Pediatric and Maternal Health Staff (PMH Staff) on the topic of PSP preparation and review, and how to optimize such interactions to facilitate a timely and efficient PSP review. As FDASIA mandated additional involvement of the PMH Staff in reviewing PSPs and associated amendments, it is very important that sponsors have the opportunity to initiate direct interaction with PMH Staff to discuss proposed studies. PhRMA recommends that FDA include PMH Staff in meetings with review divisions on a regular and consistent basis and reflect this in the PSP guidance by clearly describing a process for initiating 3-way communications (i.e., sponsor/review division/PMH Staff). In order to clarify that sponsors are encouraged to contact both the review division and the PMH Staff, PhRMA proposes that FDA revise the text in Footnote 3 to read, “In addition to consulting guidance, sponsors are encouraged to contact the specific CDER/CBER review division and the Pediatric and Maternal Health Staff to discuss specific issues that arise during preparation of the initial PSP.” For clarity, FDA should also consider moving this text from a footnote to the main text.

B. Introduction: Comment on Reference to PREA and BPCA

In Section I, “Introduction,” FDA briefly references the draft guidance entitled “How to Comply With the Pediatric Research Equity Act”. PhRMA notes, however, that the referenced draft guidance is nearly eight years old and as such does not reflect the current version of PREA. In addition, PhRMA notes that the draft guidance on PSPs does not reference the current version of BPCA or existing FDA guidance on BPCA. For greater clarity, PhRMA recommends that the PSP guidance state that it does not contain a discussion of general requirements for pediatric

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4 See Section 505B(e)(6) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as amended by Section 506 of FDASIA (Public Law 112-144, July 9, 2012).
5 See Line 34 and Footnote 3.
8 Best Pharmaceuticals for Children Act (Public Law 107-109, January 4, 2002) as amended by FDAAA (Public Law 110-85, September 27, 2007) and FDASIA (Public Law 112-144, July 9, 2012).
drug development under the BPCA\textsuperscript{10} (similar to the PREA reference in Lines 36-38) and reference the existing BPCA guidance.\textsuperscript{11} In addition, FDA should consider updating both the BPCA and PREA guidances, and ensure that the guidances on PSPs, PREA, and BPCA are consistent with one another.

To provide greater clarity on the interactions between BPCA and PREA, FDA should consider revising the PSP guidance to describe the Agency’s expectations (see Section E.1. below for additional comments on this issue).

C. Clarification of Section III: Applications that Require Submission of an Initial PSP

PhRMA suggests that FDA provide greater clarity on whether a sponsor is required to submit a PSP as described under FDASIA for a compound that is being developed specifically for a pediatric population.

In addition, PhRMA believes there needs to be greater clarity around instances where a PSP is not required.\textsuperscript{12} Specifically, PhRMA recommends that the guidance specify FDA’s current position that a PSP is not required for Orphan designated products/indications.\textsuperscript{13} PhRMA further recommends that FDA provide clarity on the relationship and timing of filing for Orphan designation and filing a PSP.

FDA should also clarify the applicability of the requirement for submission of a PSP to products that had previously been granted a waiver or deferral for pediatric development prior to implementation of FDASIA in July 2012. PhRMA believes that this section could provide greater clarity to sponsors on whether a waiver or deferral request needs to be re-submitted to FDA, and whether a new PSP is required in this case.

D. Clarification of Section IV: Timing of a PSP Submission and Comment on PSP Review Process

PhRMA welcomes earlier more formal agreement on PSPs. However, PhRMA believes that there is still a disconnect between timing of FDA’s agreement on a PSP and, where applicable, final waiver/deferral decisions. We recommend that FDA address this issue to ensure that earlier PSP agreements ultimately translate into earlier or more efficient pediatric product development.

\textsuperscript{10}Best Pharmaceuticals for Children Act (Public Law 107-109, January 4, 2002) as amended by FDASIA (Public Law 112-144, July 9, 2012).
\textsuperscript{11}FDA Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act, September 1999.
\textsuperscript{12}See Lines 98-100.
\textsuperscript{13}See FDA Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, September 2005, Section B.2.
PhRMA notes that the draft guidance does not provide details on the timeline and review process for the agreed initial PSP and any subsequent PSP amendment(s) as outlined in Section 506 of FDASIA.14

First, it would be helpful for FDA to clarify the timeline and outline the process for review of a PSP and any amendments by a review division and the Pediatric Review Committee (PeRC), including the PSP process for pediatric development programs for which FDA guidance was previously received. Specifically, PhRMA recommends that the guidance include a description and a flow chart of the FDA’s 210-day review and agreement process leading to the “Agreed Initial Pediatric Study Plan.”15 Further, the Agency should provide guidance on the PSP negotiation phase (i.e., the 90 days between when a sponsor receives feedback on the initial PSP or a PSP amendment) and when a sponsor is required to submit the “Agreed Initial Pediatric Study Plan.” Considering the limited 90-day “negotiation” period, it would be helpful if the guidance specifically address timing of FDA responses to sponsor requests for clarification during this period. PhRMA recommends that FDA consider timely formal and/or informal interactions with sponsors, e.g., a meeting to be held within 30 days of being requested. This time frame would allow sponsors and FDA to meet the 90-day timeline for reaching and documenting agreement on the initial PSP.

Next, PhRMA recommends that FDA clarify whether the review process (i.e., FDA’s timeline of 210 days) can be expected for amendments to the PSP, similar to the initial PSP. PhRMA suggests that FDA consider expedited review of certain PSP amendments as outlined below in Section F. It would be also helpful for FDA to clarify whether an existing PSP needs to be amended prior to submission of a supplement/application if the information that needs updating in the PSP is unrelated to the application being submitted.

Lastly, FDA should clarify procedures for communicating non-agreement to a sponsor. Specifically, reasons for non-agreement should be clearly communicated by FDA. In addition, PhRMA recommends that the guidance describe expectations regarding requests for PSP withdrawal and the associated timelines if withdrawals would be allowed in the process.

In addition to the above comments, PhRMA would like to recommend the following line-by-line comment:


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14 Sections 505B(e)(3) and 505B(e)(5) of the FD&C Act as amended by Section 506 of FDASIA (Public Law 112-144, July 9, 2012).

E. Clarification of Section V: Contents of the Initial PSP

1. General Comments about the PSP Content Recommendations

As written, the draft guidance is not clear on whether separate PSPs are needed for each indication, dosage form, and route of administration. PhRMA recommends that FDA address inconsistencies in the draft guidance around this issue. Specifically, Section V states that all pediatric information should be submitted at the time of initial PSP\textsuperscript{16} however, Section V.12 includes guidance to submit information on “any clinical investigations conducted under an IND for an indication other than the indication that is the subject of the initial PSP...”\textsuperscript{17} For a drug or biologic that has multiple indications, dosage forms and/or routes of administration, it would be helpful for FDA to clarify whether PSPs are specific to each indication, dosage form, etc., or intended to be a single plan that is amended with additional indications, etc., as needed.

In addition, PhRMA recommends that FDA address the relationship between a PSP and a Proposed Pediatric Study Request (PPSR)/Written Request under the BPCA.\textsuperscript{18} PhRMA suggests that FDA include the clarifying text as outlined below in the line-by-line comments for Lines 151 and 359.

In addition to the above general points, PhRMA would like to make the following line-by-line comments in this section:

<table>
<thead>
<tr>
<th>Lines 137-140</th>
<th>PhRMA suggests that FDA provide example(s) of a sufficient justification for not including detailed outline of a planned pediatric study(ies).</th>
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<tbody>
<tr>
<td>Lines 147-148</td>
<td>PhRMA suggests that when amendments to the PSP are necessary based on additional data from Phase 3 studies in adults, there should be a mechanism for expedited review of PSP amendments. FDA should outline criteria and a mechanism for expediting reviews of PSP amendments resulting from additional data from Phase 3 studies in adults (see also Section F below).</td>
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<tr>
<td>Line 151</td>
<td>PhRMA suggests that FDA consider addressing the relationship between a PSP and a Proposed Pediatric Study Request (PPSR)/Written Request under the BPCA by inserting the following text at Line 151:</td>
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> “Earlier dialogue on a comprehensive pediatric development plan, including both required research and potential pediatric uses under BPCA, is intended to result in a more efficient pediatric drug development process. Toward this end, while not a required component of the PSP by statute, sponsors may include information in the PSP to support plans for submission of future Proposed Pediatric Study Requests (PPSR/Written Request), as appropriate. Therefore, in addition to the required components

\textsuperscript{16} See Lines 142-150.
\textsuperscript{17} See Lines 353-358.
\textsuperscript{18} Best Pharmaceuticals for Children Act (Public Law 107-109, January 4, 2002) as amended by FDASIA (Public Law 112-144, July 9, 2012).
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 PPSR and ultimately issuance of a Written Request under BPCA.”

| Lines 154-160 | PhRMA recommends that FDA consider inserting the following sentence after Line 160: “Where available, the sponsor should provide evidence and assumptions on key differences between the disease in adults and in the pediatric population.” |
| Lines 164-171 | For greater clarity, PhRMA recommends that FDA consider revising 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). 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 FD&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 be included in the overview as appropriate…” |
| Lines 173-197 | PhRMA welcomes the inclusion of information on extrapolation and modeling and simulation. However, FDA should clarify with examples the types of approaches acceptable to the Agency. PhRMA recommends that FDA address the extrapolation of pharmacokinetics (PK) and pharmacodynamics (PD) in adults to the pediatric population. |
| Lines 216-221 | PhRMA recommends that FDA consider listing feasibility as a topic to be addressed under “Planned Pediatric Clinical Studies,” because it is often one of the most critical factors in successfully executing and completing these studies. FDA should clarify whether or not the expectation is for all nonclinical studies to be included in the Table or only those relevant to pediatric development. |
| Lines 239-240 | PhRMA recommends that in addition to referencing capsules and tablets, the draft guidance reference all appropriate product formulations, e.g., injectables. |
| Lines 247-248 | PhRMA recommends that in addition to drug-specific information, FDA consider public information on products from the same class as the acceptable justification for not conducting additional nonclinical studies. FDA should also consider referencing specific guidances to clarify the |
Lines 264-266

<table>
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<th>adequate rationale for not conducting additional nonclinical studies.19</th>
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<tr>
<td>PhRMA recommends that FDA consider addressing the use of modeling and simulation in dose selection and data analysis. In addition to clinical data, PhRMA recommends that FDA consider listing other data sources and types that may be acceptable to support the design and initiation of pediatric studies and revise the text to read, “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, for other conditions, in earlier studies, or a brief summary of the modeling and simulation approaches which will be used for study design and appropriate pediatric dose selection.”</td>
</tr>
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Line 297

| PhRMA notes that, at the time of the initial PSP, it is likely that only key inclusion and exclusion criteria will be definable. PhRMA recommends revising the bullet point to read “Key inclusion and exclusion criteria for the study”. |

Lines 317-325

| PhRMA notes that given the FDA Pediatric Study Decision Tree,20 efficacy studies are not always necessary, as sometimes PK studies are sufficient. PhRMA recommends that the guidance reference the FDA Pediatric Study Decision Tree. PhRMA also recommends that FDA consider inserting “if applicable” after “Efficacy/safety studies” in Line 322. |

Line 356

| As written, the statement “A summary of any agreement with other regulatory authorities also should be included” is too broad to be informative. For clarity, PhRMA recommends revising the text to read, “A summary of any pediatric drug development agreements with other regulatory authorities also should be included.” |

Line 357

| FDA should clarify whether the phrase “a summary of any clinical investigation” in Line 357 refers to any clinical studies in other adult indications, other pediatric indications, or both. |

Lines 357-358

| For greater clarity and consistency with the text regarding Written Requests in Lines 166-171, FDA should consider revising the text to read “If a sponsor plans to submit a proposed pediatric study request (PPSR) asking the FDA to issue a Written Request in the future, a summary of any clinical investigation conducted under an IND for an indication other than the |

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20 See FDA Pediatric Science and Research Activities, Figure 1, FDA Pediatric Study Decision Tree (http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106614.htm) ; Dunne, J., Rodriguez, W.J., Murphy, M.D., et al. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs, 2011 Pediatrics 128(5):e1242-e1249.
To provide greater clarity on the relationship between a PSP and a proposed pediatric study request (PPSR) / Written Request under the BPCA, FDA should consider including the following new optional Section V.13:

“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 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, and available information for any additional proposed clinical studies (e.g., PK, safety and effectiveness).”

2. Specific Comments about Section V.4 Request for Drug-Specific Waiver(s) and Section V.11 Plan to Request Deferral of Pediatric Studies

PhRMA recommends that FDA ensure consistency of this guidance on PSPs with the FD&C Act and previously issued guidance on requests for waivers or deferrals for pediatric development. According to the draft guidance on PSPs, requests for waivers or deferrals will not be formally granted or denied until the application or drug is approved (see Lines 207-208 and 347-349, respectively). These statements seem to be inconsistent with the language of the FD&C Act which requires either pediatric data, a waiver, or deferral in order for an application to be eligible to be submitted for approval. Therefore, PhRMA recommends that FDA consider including a statement in the guidance that, as long as the waiver/deferral is agreed upon in principle in the PSP, then that is sufficient for sponsors to fulfill the requirement to submit data unless ‘waived’ and, therefore, would not trigger potential Refuse-to-File issues for the affected application.

In addition, we recommend that FDA clarify which specific section(s) of the PSP are required to be completed if the sponsor plans to request a full waiver.

Further, FDA should describe how changes to an agreed-upon initial PSP with respect to the granting of deferral or waivers will be communicated to the applicant before or at the time of

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22 See Section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
approval. For clarity and consistency, FDA should consider including guidance on requests for waivers or deferrals for products that had previously been granted a waiver or deferral for pediatric development prior to implementation of FDASIA in July 2012 (see also Section I.C above).

In addition to the general points above, PhRMA would like to provide the following line-by-line comments:

| Lines 201-208 | FDA should clarify whether the PSP containing a section for requesting waiver(s) negates the need to file a formal waiver request as outlined in the draft guidance on How to Comply With the Pediatric Research Equity Act, given the information needed in this section is very similar if not the same as what needs to be submitted in a waiver request.

PhRMA recommends that FDA consider adding the following statement at Line 209:

“If a Sponsor intends to submit a full or partial waiver request and has not done so prior to 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.”

PhRMA also recommend that FDA clarify what is meant by “the above criteria” in Line 202.

| Lines 207-208 | As written, the sentence implies FDA will not act on the decision to grant a waiver until the application is approved. However, the draft guidance on How to Comply With the Pediatric Research Equity Act notes that, “[d]ecisions to waive the requirement for submission of pediatric assessments that are made 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. A waiver decision becomes final once issued in the approval letter for an NDA, BLA, or supplement.”

PhRMA recommends that FDA ensure consistency with the draft guidance on How to Comply With the Pediatric Research Equity Act by revising the sentence in Lines 207-208 to read:

“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

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24 Id. at 12.
| **Lines 341-345 and Footnote 33** | PhRMA notes that while Lines 341-345 discuss reasons for which FDA may grant a deferral of required pediatric studies, Footnote 33 discusses what a sponsor must submit with a marketing application. PhRMA recommends that the text is revised for clarity. |
| **Lines 347-349** | As written, the sentence implies FDA will not act on the decision to grant a deferral until application is approved. However, 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 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.²⁵ PhRMA recommends that FDA ensure consistency with the draft guidance on *How to Comply With the Pediatric Research Equity Act* by revising the sentence to read: “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).” |

**F. Clarification of Section VI: Contents of Requested Amendment to an Initial PSP**

PhRMA notes that the draft guidance provides minimal information regarding the submission and review of amendments to an agreed-upon initial PSP. The PMHS Standard Operating Procedure (SOP) for review of PSPs and Written Requests by the PeRC describes a 210-day review procedure that mirrors that of the initial PSP submission.²⁶ To make the guidance as comprehensive as possible and for consistency with the SOP, PhRMA recommends that FDA modify the guidance to note that the timeline for review and action on a PSP amendment is the same as for an initial PSP. In addition, PhRMA recommends that FDA consider expedited

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review of certain PSP amendments (e.g., PSP amendments resulting from additional data from Phase 3 studies in adults), and outline criteria and a mechanism for expediting reviews of such PSP amendments. PhRMA also recommends that the guidance describe how amendments to an agreed PSP that are submitted less than 210 days prior to marketing application will be handled by FDA, including if such amendments can be submitted with the marketing application or after the submission of the marketing application.

Further, FDA should clarify the circumstances under which a PSP amendment is warranted. In addition to the examples cited in the draft guidance, FDA has also cited in the past removal/addition of one or more clinical studies from the plan, changes to the nonclinical program, and changes in plans for formulation development as warranting a PSP amendment.

Also, as noted in Section B.1 above, FDA should clarify whether new indications, dosage and/or routes of administration would warrant an amendment to an initial PSP, or a new PSP.

G. Comments on PSP Format and Submission

As required by Section 503 of FDASIA, FDA recently published an internal SOP for review of PSPs and Written Requests by PeRC.27 The internal FDA SOP states that sponsors should submit the initial and amended PSPs in both PDF and Word formats to facilitate PeRC review. However, the draft guidance does not contain this recommendation. FDA should ensure consistency between the Agency SOPs and guidance documents. Therefore, we recommend that FDA modify the draft guidance (and the Initial PSP template in Appendix 2) to include the recommendation that initial PSPs and PSP amendments be submitted as both PDF and Word versions.

In addition, FDA should modify the draft guidance to indicate where the proposed initial PSP, agreed PSP and its amendments should be submitted within the eCTD structure. Also, we recommend that the draft guidance provide standard language for submission cover letter headers and provide clarification regarding the classification of the submission type (i.e., on FDA Form 1571).

In addition to the general points above, PhRMA would like to provide the following line-by-line comment.

| Line 371 | The draft guidance states that “A copy of the agreed-upon initial PSP with the requested change(s) shown in red” should be submitted. Changes shown in red will not always be clear (for example deletions) and will not show up in print (if printed in black and white). For clarity, PhRMA recommends modifying the bullet to read: “A copy of the agreed-upon initial PSP with the requested change(s) clearly marked (e.g., strikethrough text for deletions, underlined/red text for insertions).” |

27 Id.
II. CONCLUSION

In summary, PhRMA commends FDA for providing guidance on content and processes for PSPs intended to facilitate and expedite development and review of new drug and biologic products for pediatric populations.

PhRMA appreciates the opportunity to submit these comments and hopes the Agency will find them helpful in the development of the final guidance document. We look forward to a continued dialogue and collaboration with FDA and all stakeholders on issues related to pediatric drug development and implementation of FDASIA for pediatric patients. If you need further clarification on any feedback provided here, please do not hesitate to contact us.

Respectfully submitted,

Lucy Vereshchagina, PhD
Senior Director, Scientific & Regulatory Affairs
PhRMA