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July 17, 2023

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

Re: Docket No. FDA-2005-D-0460-0008 Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations Guidance for Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the Agency's **Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations** guidance for industry.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

Sincerely,

/s/
Sam Gunter
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

BIO thanks the Agency for providing updated and comprehensive guidance on PREA and BPCA.

General Comments:

- Guidances that are expected be read in conjunction would benefit from a common structure that allows quick cross-reference by the reader. BIO requests FDA to consolidate and clarify **Pediatric Drug Development: Regulatory Considerations — Complying with the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act** and the **Pediatric Drug Development Under the Pediatric Research Equity Act and Best Pharmaceuticals for Children Act: Scientific Considerations** guidances for industry to ensure stakeholders have a common understanding of the various policies and regulatory schemes.
- It is not clear what triggered references to other guidances in the draft guidance. In some sections existing ICH guidelines relevant for pediatric development are referenced while in other sections only FDA Guidance or CFR references are provided. Sponsors may get a more comprehensive overview if a more systematic approach were applied when the draft guidance references other guidance.
- An explanation from the FDA on how they intend to align with other health authorities on pediatric plans would be helpful. It is well documented that the patient population is difficult to study; any alignment or mechanisms for how to reach this alignment across the regions would be useful.
- FDA uses the term “neonates” or “neonatal” throughout the draft guidance. Instead, we recommend “term newborn infants” (0 to 27 days) to align with FDA’s guidance with the below age ranges in ICH E11(R1), which is consistent with the age ranges in FDA guidance **E11 Clinical Investigation of Medicinal Products in the Pediatric Population** (December 2000). We also recommend that the introduction or background section of the guidance specify the following age groups in the pediatric population list as described in ICH E11(R1):
    - Preterm newborn infants
    - Term newborn infants (0 to 27 days)
    - Infants and toddlers (28 days to 23 months)
    - Children (2 to 11 years)
    - Adolescents (12 to 16-18 years (dependent on region))

LINE-BY-LINE RECOMMENDED EDITS (If needed)

SECTION/LINE	ISSUE	PROPOSED CHANGE
I. Introduction (Section 1)		
II. Background		
64-66	Bioavailability is not the only consideration when contemplating pediatric formulations.	It would be more appropriate to state: "…may result in pediatric patients taking extemporaneous formulations where bioavailability, **quality, purity and potency may be negatively impacted."**
III. **Legislative and Regulatory Context**		
A. PREA		
88-89	It is suggested to incorporate the language in footnote #15 into the paragraph rather than as a footnote. It should be clear that orphan designation does not automatically waive the need to conduct pediatric cancer studies. It should also be clarified in this section that PREA still applies if the disease is rare in pediatrics but not orphan in adults.	"There are certain exceptions; for example, PREA requirements generally do not apply to a drug for an indication for which orphan designation has been granted; however, under section 505B(k)(2) of the FD&C Act, this 'orphan exemption' does not apply to products that trigger PREA under section 505B(a)(1)(B) of the FD&C Act."
91-98	This section discusses regulatory considerations rather than scientific considerations.	Consider deletion, as this topic is discussed in the other guidance under draft.
98-101	Pediatric age range may also be limited by whether an age-appropriate formulation can be developed.	The appropriate pediatric age ranges to be studied may vary, depending on, for example, the pharmacology of the drug, the incidence, and the manifestations of the disease in various age groups, **whether an age-appropriate formulation can be developed**, and the ability to measure the response to therapy.

103-104	This statement may be read as implying that the data must be generated in the actual age group for which that assessment is required.	As such, the statement undermines the use of pediatric extrapolation as outlined in ICH E11A. While there must be an appropriate age formulation, there may be circumstances where the data can be generated in another age group and extrapolated to the target age group.
107-109	This is a direct quotation from the regulations; however, it does not reflect the current language of reference and target population (as extrapolation can be between two pediatric populations).	It is recommended that the language of ICH E11A be woven into this statement to be consistent. We recommend replacing "adults" with "reference" and replacing "pediatric patients" with "target population." https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation
136-141	Original text: "PREA requirements generally do not apply to a drug for an indication for which orphan designation has been granted; however, this orphan exemption does not apply to drugs that trigger PREA under section 505B(a)(1)(B) of the FD&C Act. Accordingly, for such drugs meeting the criteria in section 505B(a)(1)(B), the requirement to submit reports on the molecularly targeted pediatric cancer investigation applies even if the drug is for an adult indication for which orphan designation has been granted." To further explain what is meant by the term "trigger" in the guidance text, we believe it would be helpful if FDA	We recommend the following revision: "PREA requirements generally do not apply to a drug for an indication for which orphan designation has been granted; however, this orphan exemption does not apply to drugs that trigger PREA under section 505B(a)(1)(B) of the FD&C Act. Accordingly, for such drugs meeting the criteria in section 505B(a)(1)(B), the requirement to submit reports on the molecularly targeted pediatric cancer investigation applies even if the drug is for an adult indication for which orphan designation has been granted. For such drugs that do not meet the criteria in section 505B(a)(1)(B) (e.g., FDA has placed the molecular target on the non-relevant list) and for which orphan designation has been granted, then standard PREA applies, and sponsors accordingly are exempt from PREA requirements." "

	acknowledged that if the Agency determines that the molecular target is on the non-relevant list and the indication has orphan designation, standard PREA applies and the sponsor is exempt from PREA requirements.	
B. BCPA		
153-156	This section could be improved with additional clarification that the sponsor can submit a PPSR for a non-orphan indication for children. For example, if the drug was approved for a certain indication in adults and the sponsor proposes to study a pediatric-only indication that is not necessarily orphan.	"FDA may issue a WR for pediatric studies either in response to a proposed pediatric study request (PPSR) or at the initiative of FDA. A WR or PPSR can be for non-orphan indications in pediatric patients."
166-169	We believe that the FDA was not granted authority under BPCA and/or PREA to deny a WR because a study is a requirement under PREA. The law specifically states: SEC. 505A.(b)(1) "the Secretary determines that information relating to the use of a new drug in the pediatric population may produce health benefits in that population..." ANY drug with any study requirements under PREA meets this definition, and thus the Agency does not have the discretion to deny a WR on these grounds. In addition, this is not consistent with observed regulatory precedence.	The policy to not issue WR based on PREA studies alone is a major change and is not justified based on data included in the guidance. There are several products that can only be used to treat a specific condition, such as HIV, and cannot be developed to treat any other condition. The current change in policy makes such products no longer eligible to seek incentives. This change will have a major impact across therapeutic areas and significantly impact pediatric drug development. The observation that PREA has resulted in more labeling changes than BPCA does not support the change in position that FDA will only issue WRs for additional studies beyond those required by PREA. If the PREA required studies exhaust the indications in which there is a meaningful health benefit for a pediatric patient, and the sponsor submits a PPSR, a WR should be issued. The language used in the cited USC 355a is "may"

		(allowing WRs for PREA-required studies) and not "must" (not precluding WRs or associated exclusivity for PPSRs) which does not support the FDA position as stated in this draft guidance.
C. The Pediatric Review Committee		
VI. Scientific Considerations for Pediatric Drug Development		
187-191	The sentence that begins this section ("In general, principles that guide pediatric drug development …") may send the wrong message if the technical details and ethical considerations are not delineated. While the assessment of the benefit risk may follow the same principles, pediatric drug development is governed by additional ethical principles that can make the drug development program look different than for adults. For example, if there is no scientific necessity to conduct studies in pediatrics, it is unethical to conduct studies altogether in pediatric patients. Additionally, if the pharmacokinetic (PK) properties of the investigational product are substantially different in patients than healthy volunteers, conducting single dose PK studies in pediatrics is typically not allowed.	We propose revising the statement to indicate that the assessment of benefit risk ratio follows the same principles with additional considerations as in adults or deleting the statement.
193	Original text:	We recommend the following revision:

	"The information needed to approve a drug for pediatric use includes data from nonclinical studies, and clinical dosing, safety, and effectiveness information." This text implies that FDA requires that data from nonclinical studies are necessary to support pediatric approval. However, we believe that it is not always necessary.	"The information needed to approve a drug for pediatric use may include ~~includes~~ data from nonclinical studies, and clinical dosing, safety, and effectiveness information."
196-198	The draft guidance states, "Finally, applicants should determine whether existing data from adult human studies or animal disease models can be used to support both the safety and preliminary effectiveness of the drug sufficiently to initiate pediatric studies."	It would be useful here to cite the FDA draft guidance on the ethical principles guiding pediatric research, specifically the section on establishing a prospect of direct benefit under 21 CFR 50.52. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children
206-208	It is important to clarify that during early phases of development, the sponsor may not be able to determine relevant details as part of the iPSP, such as doses to be studied.	We suggest general guidance/an example on how to approach these sections.
A.	**Considerations Regarding Data in Pediatric Patients**	
219-281	We appreciate that this section of the guidance provides information on formulation development. We believe that additional guidance specific to each pediatric age range, such as information on acceptable dosage form and size and what would be deemed as a palatable	We suggest clarifying in this section the following: • Guidance on developing formulations for the various pediatric age ranges. • Whether the sponsor can directly test the formulation in pediatric patients or rely on a pilot PK study in adults.

	dosage form, would be helpful particularly for synthetic drug product development. This section is also lacking when a PK bridging study for the pediatric formulation is needed. It would be helpful if FDA clarified this in this section.	• When should the sponsor develop the pediatric formulation.
224-227	Original text: "A marketing application that includes a pediatric indication may need a new dosage form (e.g., a liquid rather than a tablet), addition of a new strength (e.g., tablet containing a lower dose), or several different dosage forms (e.g., drops, orally disintegrating tablets, pellets)." We recommend clarifying that a new dosage form needed for a new pediatric indication may need an age-appropriate formulation.	We recommend the following revision: "A marketing application that includes a pediatric indication may need <u>an age-appropriate formulation, which may include</u> a new dosage form (e.g., a liquid rather than a tablet), addition of a new strength (e.g., tablet containing a lower dose), or several different dosage forms (e.g., drops, orally disintegrating tablets, pellets)."
253-254	Original bullet point: "The use of excipients, including certain dyes, alcohols, flavoring agents, or preservatives, considering any potential interactions." We interpret "potential interactions" to mean those that could have an adverse impact on drug stability. We recommend	We recommend the following revision: "The use of excipients, including certain dyes, alcohols, flavoring agents, or preservatives, considering any potential interactions <u>(i.e., interactions impacting drug stability)</u>."

	the proposed change to provide additional clarity.	
256-257	Original bullet point: "The use of a delivery device (e.g., dropper, syringe, measuring cup) co-packaged with the formulation." The statement is not clear if FDA is suggesting that a delivery device be co-packaged with the formulation.	We recommend the following revision: "The use of a delivery device (e.g., dropper, syringe, measuring cup), if co-packaged with the formulation."
264	Compatibility & stability should also take into consideration drug with the proposed delivery device.	We recommend the following revision: "The compatibility and stability assessments of the drug substance with the proposed excipients (and/or delivery device) under storage conditions during marketing and in-use conditions."
275-277	Original bullet point: "The performing of dissolution/release testing using standard dissolution media as well as media mimicking in vivo gastric fluids and environment (such as media containing milk for neonate and infant studies)." As gastric fluid volume and pH is significantly different for different age groups, we recommend stating that the dissolution/release testing performed *in vivo* should be considered according to the appropriate age range.	We recommend the following revision: "The performing of dissolution/release testing using standard dissolution media as well as media mimicking in vivo gastric fluids and environment (such as media containing milk for neonate and infant studies) as appropriate according to the age range."

293	The draft guidance states, "…toxicities that are not assessed in reproductive toxicity testing and that may not be safely…"	We recommend that the draft guidance should include a discussion of the role of enhanced pre- and post-natal development (ePPND) studies in assessing potential neonatal toxicity.
302	ICH S11 has extensive guidance on when juvenile animal studies may be required and how to design the appropriate study and should be referenced here.	We suggest including a reference to ICH S11, in addition to those listed in footnote 46.
340	Guidance regarding inclusion of different age groups in PK studies will be helpful when designing early-phase studies.	We suggest that FDA provide guidance regarding inclusion of different age groups in PK studies when designing early-phase studies.
342-343	Original bullet point: "The sample size for PK studies should be justified, taking into account the expected variability in PK parameters for that age group." Given that the recruitment of pediatric subjects may be difficult for certain therapeutic areas, we suggest including an additional sentence stating that practical considerations may be taken into account when determining sample size, as appropriate.	We recommend that the additional sentence be added: "The sample size for PK studies should be justified, taking into account the expected variability in PK parameters for that age group. However, practical considerations based on feasibility of recruitment for pediatric subjects in certain therapeutic areas may also be taken into account when determining sample size."
349	The draft guidance states, "A dedicated PK study may not be needed in every age group."	In addition, a PK run-in could be used as the first phase of a larger clinical study (in which case it is not a dedicated PK study). We suggest that this option be included, as mentioned in the ICH E11A draft guidance (section 4.1).

		https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation
374-376	Original bullet point: "The use of bridging studies from one population to another (e.g., from adult and older pediatric age groups to younger children) including, where appropriate, the use of PD modeling." Please clarify the term "bridging study" and any recommended study design attributes as this term has nonuniform usage in drug development. It is unclear whether both populations being compared/bridged must be evaluated in the study, or whether previously generated adult or adolescent data can also be used and extrapolated for comparison purposes to demonstrate bridging.	We recommend additional clarification on the term "bridging study" for PD studies or include a reference to another guidance that provides more information.
384	The draft guidance states, "…information from administration of the drug to children is almost always needed to establish…" "almost always" undermines the ICH E11A draft guidance on the extrapolation of safety.	We recommend replacing "almost always" to "often." "…information from administration of the drug to children is ~~**almost always**~~ **often** needed to establish…"
B.	**Pediatric Extrapolation**	
C.	**Timing of Pediatric Studies**	
D.	**Drug Development for the Neonatal Population**	

491-503	In diseases that only occur in neonates, such as “neonatal acute respiratory distress syndrome”, “neonatal necrotizing enterocolitis”, etc., very little benefit, if any, will be learned from studying the drug in older children for these indications. It would therefore be justified to evaluate potential therapies for these diseases solely in neonates.	We recommend FDA provide concrete recommendations on how to overcome the significant challenges of neonatal drug development, as well as for clarification regarding FDA’s recommendation with respect to studying potential therapies for specific neonatal diseases/pathologies.