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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-0460-0007 Pediatric Drug Development: Regulatory Considerations — Complying with the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act

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: Regulatory Considerations — Complying with the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act.**

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 to be read in conjunction would benefit from a common structure that allows quick cross-reference by the reader. BIO requests the FDA 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 the Best Pharmaceuticals for Children Act: Scientific Considerations** Guidances for Industry to ensure stakeholders have a common understanding of the various policies and regulatory schemes within these documents.
- 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 insight on how to reach this alignment across regions would be useful.
- The Guidance acknowledges that BPCA and PREA are intended to work together. Pediatric Written Requests were routinely issued for studies required by PREA. The BPCA states that a WR can be issued for "information relating to the use of a new drug in the pediatric population may produce health benefits in that population." If the Agency is requiring data under PREA, they must be doing this because they believe that the product may produce health benefits in the pediatric population – if the product did not have that potential, a waiver would be granted under PREA. The Agency should consider the chilling effect on limiting the use of BCPA to only studies that are above and beyond those required under PREA.
- The policy to not issue written requests 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.
- BIO requests that the FDA more broadly allows a flexible approach. For example, the Proposed Pediatric Study Request (PPSR) may be submitted before the PSP waiver has been granted.

- The guidance document is sometimes repetitive and therefore confusing to the reader. For example, information on PREA and orphan designation and the exception regarding molecularly directed therapies is repeated in multiple sections. It would be helpful if the repeated content was streamlined.

LINE-BY-LINE RECOMMENDED EDITS

SECTION/LINE	ISSUE	PROPOSED CHANGE
I. Introduction		
II. Overview of Regulatory Strategy for Pediatric Drug Development		
Section II	We suggest clarifying how the agency defines "health benefits in the pediatric population."	We recommend including a listing of example criteria to be met to qualify for potential health benefits in the pediatric population, such as literature showing unmet medical need, use of literature or research showing therapeutic benefit in the adult/ped patient population, off label use data, safety information etc. Other guidances and documents may need to be updates as well.
A. General Approach		
63-72	Original text: "For purposes of pediatric drug development, FDA generally considers the pediatric population to include […] • Neonates: birth through 27 days (corrected gestational age) • Infants: 28 days to 23 months • Children: 2 years to 11 years • Adolescents: 12 years to younger than 17 years" We recommend that the above age ranges be revised to align with the age ranges in ICH E11(R1), which is consistent with the age ranges in FDA/ICH guidance entitled E11	We recommend the following revision: "For purposes of pediatric drug development, FDA generally considers the pediatric population to include those patients from birth to younger than ~~17~~ 18 years (i.e., birth through ~~16~~ 17 years of age), and to include the subpopulation age groups of ~~neonates,~~ preterm newborn infants, term newborn infants, infants and toddlers, children, and adolescents. Consistent with International Council for Harmonization (ICH) guidelines, FDA considers these subpopulation age groups to be divided as follows: ~~• Neonates: birth through 27 days (corrected gestational age)~~ ~~• Infants: 28 days to 23 months~~ ~~• Children: 2 years to 11 years~~ ~~• Adolescents: 12 years to younger than 17 years~~

	Clinical Investigation of Medicinal Products in the Pediatric Population (December 2000). We recommend that the terminology be revised throughout the draft guidance. Further, we believe that the pediatric age range should include those who are 17 years old and up to younger than 18 years old.	• 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))"
80	The Guidance acknowledges that BPCA and PREA are intended to work together. Pediatric Written Requests have been routinely issued for studies required by PREA. The Agency has traditionally issued WRs with studies outside of those required by PREA, but if additional data was not needed on dosing, safety and efficacy, the WR could be limited to study(ies) required under PREA. The BPCA states that a WR can be issued for "information relating to the use of a new drug in the pediatric population may produce health benefits in that population." The Agency should consider the chilling effect that only using the requirement may have on pediatric drug development. If the Agency will not grant a WR for PREA studies alone, it is important to ensure that the WR currently being executed not be rescinded if they are for PREA studies only.	We object to this new policy and request 1) a reconsideration of this approach based on its potential deleterious effect on medical product development or 2) clarification and language in the final guidance that would grandfather previously reviewed products from this new way of working.
84-89	Suggest clarifying after the sentence ending on line 89 that pediatric cancer studies may need to be conducted even if orphan designation has been granted as per section 505B(k)(2) of the FD&C Act.	"...to the growth or progression of pediatric cancer. This requirement applies even if the drug is for an adult indication for which orphan designation has been granted per section 505B(k)(2) of the FD&C Act."

115-117	The draft guidance states, "However, as discussed in Section IV. A. 2., Written Request Studies, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA." Also, for diseases that are not rare for which the drug has only one indication, there is no mechanism to obtain a WR. Given this limitation, Sponsors will only be able to achieve exclusivity if they go beyond what is required under PREA.	This approach would mean, for example, that for products that only treat one condition such as HIV, obtaining a WR is no longer feasible. This limitation may have deleterious effects on drug development and public health.
116 and 691	Line 116: "Written Request studies, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA." Line 691: "Historically, FDA has at times issued WRs solely for studies required under PREA, even if there were no other indications that may produce health benefits in the pediatric population. However, over time, data on pediatric labeling changes pursuant to BPCA and/or PREA have been collected."	This change to practice does not appear to be supported by statute.
B. Developing Drugs for Pediatric Use		
151-153	The draft guidance states, "Pediatric studies might be considered appropriate when prospects of direct benefit to the enrolled children are sufficient to justify the risks."	It would be appropriate to reference the FDA draft guidance on ethical considerations in pediatric trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ethical-considerations-clinical-investigations-medical-products-involving-children
187-192	Original text:	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 the PREA requirement for submission of reports on the molecularly targeted pediatric cancer investigation. Thus, PREA does not require submission of pediatric assessments for an application (or supplemental application) to market a drug for an 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 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.	"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 the PREA requirement for submission of reports on the molecularly targeted pediatric cancer investigation. Thus, PREA does not require submission of pediatric assessments for an application (or supplemental application) to market a drug for an indication for which orphan designation has been granted. <u>For such drugs that do not meet the criteria in section 505B(a)(1)(B) (eg, 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 are exempt from PREA requirements.</u>"
192-195	Original text: "As FDA has interpreted PREA, if orphan designation is granted after approval of a drug, and post marketing studies were required under PREA at the time of the drug's approval, the granting of orphan designation does not alter the already existing requirement for such studies."	We recommend that PREA requirements do not apply to drugs or biological products that are granted orphan designation after approval.

	This policy change disadvantages sponsors whose orphan designation is still pending at the time of approval. In addition, this policy change does not align with section 505B(k)(1) which states that PREA "does not apply" if the drug or biological product was granted orphan designation.	
204-207	The draft guidance states, "Despite this orphan exemption under PREA, a sponsor that submits an application to market a drug for an indication for which orphan designation has been granted may be eligible to qualify for pediatric exclusivity if FDA issues a WR to the sponsor in connection with the application and the sponsor accepts."	This approach is supported. However, it may be inconsistent with the statement that FDA would not issue a WR for studies required under PREA solely, as those same studies may have been required absent the orphan drug designation (ODD) (and no others).
218-225	Original text: "Many sponsors conduct their entire clinical programs in other countries and occasionally submit a marketing application with little, if any, prior interaction with FDA. All sponsors who seek to market their drugs in the United States are strongly encouraged to contact FDA as early as possible to avoid any delay in providing any required pediatric information in their applications."	FDA should clarify how sponsors should interact with review divisions in the absence of an active IND.
235-236	Original text: "FDA may consider issuance of a WR for other indications that may have health benefits in the pediatric population."	We recommend that the final or revised draft guidance include what criteria FDA will apply to determine which other indications may have health benefits in the pediatric population.

	It is unclear how the FDA will initially assess which indications may have health benefits in the pediatric population.	
III. Pediatric Research Equity Act		
A. Overview – Requirements of PREA		
B. Developing Drugs for Pediatric Use		
288-289	It would be beneficial if there is additional guidance on timing for iPSP submissions.	We suggest the guidance addresses in more detail the appropriate timing for submission of an iPSP, for example in cases where no EoP2 meeting is held (prior to pivotal study initiation).
C. Pediatric Assessments and Molecularly Targeted Pediatric Cancer Investigations Under PREA		
D. Waivers and Deferrals Under PREA		
371-420	An additional item to include in the listed criteria for a waiver is where a molecular pathway/mutation is present in some pediatric cancers but is not driving the malignant process.	We suggest editing this section to include as an additional exemption where a molecular pathway/mutation is present in some pediatric cancers but is not driving the malignant process.
572-574	With respect to PMR status that sponsors are required to provide for PREA studies, it is unclear whether this new agreed date is the baseline, or whether the original agreed date would remain the baseline.	Please clarify FDA's expectations about the baseline date regarding status assessment timelines and requirements.
Section III.D.2. (Deferrals)	FDA's use of the term "pediatric assessments or reports on the molecularly targeted pediatric cancer investigation" in this section is confusing. It appears the term likely refers to both traditional PREA ("pediatric assessments") and RACE ("reports on the molecularly targeted pediatric cancer investigations"), but it is somewhat confusing, and clarification (as suggested) would be beneficial.	We suggest that FDA clarify by revising the text: "pediatric assessments required under 505B(a)(2) or reports on the molecularly targeted pediatric cancer investigation required under 505B(a)(3), as applicable" (at least at the first use of the term).

E. Compliance with PREA		
IV. Best Pharmaceuticals for Children Act		
A. Written Requests		
641-643	Original text: "As a greater understanding of the indication or of the mechanism of action of a particular drug or drug class develops, WRs, including elements within a study or studies necessary to qualify for pediatric exclusivity, may evolve." We believe it is important that FDA clearly communicates their expectations regarding the studies that sponsors must complete to receive pediatric exclusivity. The assessment should be done based on science known at the time of the request for a WR. Since the timelines to complete these studies are tied to the patent expiry, amendments of studies based on later advancements in science not only may jeopardize the completion of the WR in a timely manner, but unfairly alter the requirements for meeting a WR based on scientific information not known when the WR was agreed. This is not consistent with the intent of the statute.	We recommend that FDA clearly communicate health benefit study requirements at the time of the WR for the studies that sponsors must complete to receive pediatric exclusivity.
694-700	This analysis misses several points: • The original exclusivity provision was established to compensate for the lack of a market driver to develop therapies in the pediatric population. While the forcing function of PREA has worked,	It would be helpful to understand the basis of FDA's analysis and conclusions. The observation that PREA has resulted in more labeling changes than Best Pharmaceuticals for Children Act (BPCA) does not support the change in position that FDA

	the BPCA and the legal bar for issuance of a WR has not been repealed. The Agency does not have the legislative authority to sideline the provisions of BPCA solely due to the successes of PREA. • Therapeutics are advancing rapidly, including the development of more biologics. As BPCA offers no additional benefit in most cases for biologics, many developers do not choose to engage with the provisions of this legislation.	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 Proposed Pediatric Study Request (PPSRs)), which does not support the FDA position as stated in this draft guidance.
704-718	Original text: "In light of the data on pediatric labeling changes pursuant to the BPCA and/or PREA, FDA believes WRs should be reserved for those sponsors who conduct additional pediatric studies — beyond what is required under PREA — that may produce health benefits in children. Thus, upon finalization of this guidance, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA." We believe that granting market exclusivity for studies conducted beyond what is required under PREA is inconsistent with the BPCA and PREA framework as described in the statute (21 U.S.C. 355a(h)), which states that written	We recommend that lines 702-718 be deleted.

	requests may consist of studies that are conducted under PREA. This policy change will disadvantage drugs from obtaining market exclusivity where the pediatric labeling changes could only be based on studies conducted under PREA.	
727-736	In the paragraph on page 22 relating to nonclinical studies, the first sentence (line 727) suggests that the WR itself can contain required nonclinical studies. The last sentence seems to indicate that if nonclinical studies are needed to determine if the clinical study could produce health benefits, then the nonclinical studies would inform whether a WR would be issued. These seem to be two different concepts and may need to be separated and expanded upon to clarify.	We recommend reviewing this section to clarify the concepts relating to nonclinical studies.
776-778	The last sentence of paragraph 2 on page 23 ("Even a minor change to a study, …") may warrant further emphasis in the document since it is not generally well known.	We suggest reviewing this paragraph and emphasizing/expanding upon the last sentence.
B. How to Obtain a Written Request		
C. How to Submit Study Reports in Response to a Written Request		
D. Qualifying for Pediatric Exclusivity		
E. Determining Eligibility for Pediatric Exclusivity		
981-983	The draft guidance states, "If FDA determines that the objectives of the WR were met, then FDA concludes that the sponsor has fairly	It is unclear whether FDA would grant pediatric exclusivity under these circumstances. Line 999-1001 can be read to imply "yes", but it is recommended that this line be more explicit.

	responded, even if it did not meet the terms of the WR."	
F. Attaching the Period of Pediatric Exclusivity After a Determination that a Drug Qualifies for Pediatric Exclusivity		
1026-1027	It is difficult to find additional guidance on where to find information on pediatric exclusivity for combination drugs.	Suggest adding a reference to appropriate documents to locate further information.
1059-1112	The draft guidance notes that "pediatric exclusivity does not attach to new (not previously listed) patents or exclusivity covering the later filed applications or supplements unless the subsequent drug product could not be labeled without the data that qualified the previously approved drug product for the prior pediatric exclusivity." (p. 31) It is not clear whether this is a substantive change in policy. It is also not clear whether this section applies to next-generation versions of approved agents (such as subcutaneous formulations) or whether FDA is stating that a sponsor may get exclusivity (6-month extension) only for the new pediatric indication resulting from the WR but not for the original adult indication for which the BLA/NDA was filed. Structurally, it would be helpful if Biological Products section was mentioned earlier, allowing Section F to be read in the context of small molecules.	We suggest requesting clarification on: • Whether this is a substantive change in policy and, if so, to please expand upon it. • Whether this section applies to next-generation versions of approved agents (such as subcutaneous formulations). • Whether FDA is stating that a sponsor may get exclusivity (6-month extension) only for the new pediatric indication resulting from the WR but not for the original adult indication for which the BLA/NDA was filed. • We would like additional clarification on future applications that the pediatric exclusivity would attach to. It appears to be a substantive change from what it was before, and it is not clear what exclusivity attaches to and will attach to. • Regarding the possible 2nd period of pediatric exclusivity and accompanying 2nd WR, we could use additional clarification, as it is not clear when/where this would be applicable. We suggest moving Biologic Products section earlier in F.
V. Elements Common to PREA and the BPCA		
A. The Pediatric Review Committee		

B. Publishing Information About Pediatric Studies		
Footnote 152	Original text (footnote #152): "On occasion, information obtained by FDA subsequent to issuance of a WR causes FDA to rescind the WR." It is unclear under which circumstances FDA would rescind the WR and how that aligns with the statute.	We recommend that FDA provides more information on what criteria would cause FDA to rescind the WR.
C. PREA and Pediatric Exclusivity		
D. Considerations for Labeling of Drug Products		
E. Adverse Event Reporting for Drug Products Subject to the BCPA and PREA		
VI. Additional Information		