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Dockets Management Staff
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-D-0760

Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials; Draft Guidance for Industry

To Whom It May Concern,

Biotechnology Innovation Organization (BIO) welcomes the opportunity to comment on the Food and Drug Administration (FDA or Agency) draft guidance for industry entitled "Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials".

We strongly support efforts to facilitate medical product development for patients of all ages within the pediatric population and applaud collaboration between our members and the Agency to navigate the unique associated nuances. Planning, conducting, and recruiting for clinical trials that involve pediatric patients can be challenging, and we applaud the Agency for providing transparency and safeguards for different age groups through this draft guidance that may benefit both industry and regulators alike, and ultimately, our youngest patients.

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.

(1) General Comments

- BIO notes that the guidance could be interpreted to be prescriptive on which tools should be used to measure growth and development, e.g., orchidometer, digital scale, etc. These tools may not be readily available in sites with fewer resources, especially in underserved communities. We suggest that the guidance clarify flexibility around what tools may be used to avoid unintended consequences, i.e., creating challenges to enrollment of a greater population of patients from such communities.
- Expanding on the topic of body proportionality (e.g., lines 365-367) would strengthen the document, especially for those rare conditions associated with disproportionate stature or measurements. For example, measures of proportionality can be listed and defined (e.g., arm span, sitting height, sitting height/height ratio, upper segment to lower segment ratio, etc.), and further guidance on the assessment of proportionality (i.e., how to measure each of these parameters) would be helpful.

- Expanding on the topic of dual-energy X-ray absorptiometry scan (DXA) (e.g., lines 365-367) to reference additional information from relevant guidelines, e.g., from The International Society for Clinical Densitometry (ISCD)[1], would be helpful. Examples include:
    - DXA lumbar spine measurements are feasible and can provide reproducible measures of bone mineral content (BMC) and areal bone mineral density (aBMD) for infants and young children 0-5 years of age.
    - DXA whole body measurements are feasible and can provide reproducible measures of BMC and aBMD for children ≥ 3 years of age.
    - DXA whole body BMC measurements for children < 3 years of age are of limited clinical utility due to feasibility and lack of normative data. Areal BMD should not be utilized routinely due to difficulty inappropriate positioning.
    - In children with short stature or growth delay, spine and total body less head (TBLH) BMC and areal BMD results should be adjusted. For the spine, adjust using either bone mineral apparent density (BMAD) or the height Z-score. For TBLH, adjust using the height Z-score.

(2) Additional Topics to Consider

BIO notes additional areas for consideration when FDA finalizes the draft guidance:

- We suggest that FDA considers adding recommendations on which timeframes offer the most meaningful data for specific growth and development measurements, e.g., clarify whether 12 months is sufficient to provide clinically meaningful information for growth and development. BIO notes that it would also be helpful to clarify the forms of efficacy and safety analysis, and associated timeframes, that FDA recommends for data collection on growth and development.
- Additional guidance regarding statistical methods for analyzing growth or pubertal developmental data could be helpful for sponsors. Similarly, we suggest that the guidance should provide more clarity about whether performing growth measurements at the same time of day is specific to each patient or for all patients generally. It may be constraining to conduct measurements for all patients at the same site at a particular time of day.
- We suggest including guidance regarding the use of stretching versus non-stretching methods to obtain height measurements. Stretching measures (e.g., gentle upward pressure on the mastoid processes during measurement) are not necessarily universally accepted.

[1] https://iscd.org/wp-content/uploads/2021/08/Best-Practices-DXA-Article.pdf

(3) Specific Comments

In addition, please consider the following table outlining comments on specific language in the draft guidance.

SECTION	ISSUE	PROPOSED CHANGE (UNDERLINE TO ADD, ~~STRIKETHROUGH~~ TO DELETE)
I. INTRODUCTION		
II. BACKGROUND		
III. MEASUREMENTS OF GROWTH AND PUBERTAL DEVELOPMENT		
Line 60-63	Asset teams are tasked with developing a manual of operations which addresses many elements mentioned here regarding collection and recording of growth parameters and pubertal development. We suggest that including this level of detail in the study protocol may be too restrictive and could potentially result in protocol deviations as there may be some variation depending on trial site location, personnel, and capabilities. Also, the guidance does not discuss who should provide training to investigator and trial site personnel.	Suggested revision: "Develop ~~a protocol for~~ training <u>for</u> investigators and trial site personnel…". Also, we suggest that the training of investigators and trial site personnel should be provided by individual(s) with expertise in growth and pubertal status assessments.
Lines 70-71	It is unclear whether this language should be interpreted to mean that growth parameters should be collected for studies 12 months or more in duration, whereas collection of growth parameters for studies less than 12 months in duration should be discussed with appropriate review division, or if study duration is less than 12 months, then collection of growth parameters not required. We agree that collection of growth parameters is study/asset/drug class-specific but would consider this to be reasonable high-level guidance.	Suggested revision for clarification: "Collection of growth measurements is required for clinical studies with a duration of 12 months or longer."
Lines 70-73	The guidance does not discuss the frequency or timing of growth assessments.	We suggest the guidance indicate that the collection and recording of growth assessments should be performed every 3 to 6 months.
Lines 75-77	FDA is requested to consider providing additional guidance in cases where patient stops the study drug and starts a new therapy (e.g., biologic) and patient's measurements continue to be collected.	We request additional clarity on how growth (as well as efficacy and safety) assessments should be made.

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	For example, if growth retardation is observed 52 weeks after discontinuation of the study drug and 48 weeks after starting a new treatment, it is unclear whether the event should be attributed to the study drug or the new therapy.	It would be helpful to clarify whether any growth event should be attributed to the study drug or the new therapy, what timeline should be applied to guide analysis for safety events, etc.
Lines 75-78	We suggest that this language may be too restrictive as continued data collection and enrollment for patients who discontinue study drug is dependent on study design and obviously patient consent. We would find this particularly troublesome for studies with 4-5 year (or longer) long-term extensions for these aforementioned reasons.	Suggested revision: "As appropriate, keep pediatric participants who discontinue the study treatment…".
Lines 77-78	Measurements obtained after treatment discontinuation may be useful for ensuring the reliability and interpretability of analyses and results.	We suggest that FDA comment on how growth should be assessed, and for what timeframe, after discontinuation of study drug and after the five half-lives of study drug are eliminated. For example, it would be helpful to clarify whether a decrease in the rate of growth would then be attributed to study drug. There could also be scenarios when the patient starts another drug after discontinuation of study.
Lines 82-83	We suggest that addressing these items at a high level in the protocol is appropriate but are concerned with providing too much detail in the study protocol regarding these items.	Suggested revision: "To reduce measurement error, the sponsor should ~~include procedures and practices in the protocol~~ provide guidance for consistent growth parameter collection, such as the following:".
Lines 85-86	Sponsors can provide high level guidance; however, calibration frequency, monitoring, and maintenance differs by scale/equipment manufacturer.	We suggest flexibility on this topic.
Lines 93-95	The guidance does not discuss the need to have one blinded individual perform height assessments to ensure consistency and reduce variability in growth assessments.	In general, it is preferable that the collection and recording of growth assessments be performed by the same blinded and suitably trained individual. Alternatively, whenever possible, the same trial health care professional should perform and record growth assessments (same language as pubertal assessments).
Line 97	Because of diurnal variations in height and weight, schedule study visits and/or perform	Suggested revision:

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	growth measurements at the same time of day unless justification is provided.	"…optimally perform growth measurement at the same time of day unless justification is provided." In trials where growth is a secondary endpoint, we suggest some flexibility be offered as requiring visits at the same time of day may be a significant inconvenience for families.
Lines 135-137	The guidance does not discuss the need to plot measurements according to months or years and months.	Care should be taken to ensure age in months or age in years and months is accurately captured when plotting growth measurements on standardized charts.
Line 145	"Two years of age and older, use the Centers for Disease Control and Prevention (CDC) growth charts."	It would be helpful to clarify whether the guidance is suggesting that each patients growth is plotted on a growth chart.
Line 161	For trials conducted outside the United States, sponsors should use growth charts based on normative data for the trial population, when available	We suggest that muti-national trials should have the option of using CDC growth charts to standardize data.
Line 167-177	We believe this level of detail is inappropriate to include in the study protocol. We note challenges for sites if asked for more calibration than is required by scale manufacturers.	We suggest clarifying that relying on specific guidelines from manufacturers is acceptable.
Line 229	Linear Growth (Length and Height) Assessment	It would be helpful if FDA could comment on the best methodology to assess growth.
Lines 230-248	Sponsors sometimes meet resistance when requiring wall-mounted stadiometers since sites cannot be required to alter their property (i.e., fixing a wall-mounted instrument).	Please consider clarifying that flexibility around wall mounting may be acceptable.
Lines 240-241	Having both length and height measures taken as growth marks might create conflicting data. Moreover, standing height is preferable as it tends to be more accurate. However, during this transition phase, individual child development and investigators' professional expertise and experience might play a role in deciding which method is most suitable.	Suggested revision: "When transitioning from recumbent length to standing height measurements in participants between 2 to 3 years of age, ~~measure both length and height~~ sponsors should allow investigators to decide which method to choose. Standing height is preferred but investigators should judge based on their professional expertise and on the child's individual development."

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Lines 245-247	Before measuring linear growth, remove shoes, hats, hair ornaments, and braids whenever possible because these items can interfere with accurate linear growth measurement.	Suggested revision: "[…] will interfere with accurate linear growth measurement. <u>If it is not possible to remove hair ornaments or braids, document their presence to help to explain subsequent possible variability.</u>"
Lines 249-259	The guidance does not discuss the acceptable variability between measurements.	We suggest the guidance include a discussion of acceptable variability between measurements, e.g., 0.3 cm.
Lines 252-253	"Repeat measurements that are not clinically plausible (e.g., height measurement that is lower than the height measured at the previous or prior study visits)." Certain pathologies may need to be considered.	Suggested revision: "Repeat measurements that are not clinically plausible (e.g., height measurement that is lower than the height measured at the previous or prior study visits)<u>, unless potentially related to underlying pathology, e.g., fracture of vertebrae, progressing scoliosis, etc</u>."
Line 261	Details of alternative strategies for measuring/evaluating linear growth may be better suited for an alternative document (e.g., manual of operations) as opposed to the study protocol.	Suggested revision: "Provide ~~details in the protocol~~ <u>guidance and/or instruction</u> on any alternative strategies that will be used for evaluating linear growth in trials enrolling pediatric participants with conditions that may affect measurement of linear growth […]."
Lines 264-266	The adjustment strategy discussed is unclear around whether it should be applied only when the indication involves participants who all have conditions that impact growth, e.g., contractures, skeletal dysplasia, scoliosis, etc.	We request FDA to expound on what is meant by having to provide alternative strategies in the protocol for pediatric participants with conditions such as contractures, skeletal dysplasia, scoliosis, etc. The WHO site that was cited in the draft guidance leads to various documents that discuss methods for adjusting for kurtosis and skewness. It is not clear if this is the same type of adjustment the FDA recommends the protocols to explain as well. Similarly, it would be helpful for the guidance to include

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		recommendations on situations where some rather than all pediatric participants in a study have such conditions and could potentially skew the collected growth and development data.
Lines 307-329	Tanner Staging can be difficult to evaluate depending on indication. Similarly, self-assessment in Tanner Staging may be a viable option to address the culturally diverse views regarding physical examination and could encourage participation from certain groups	We recommend clarifying that using self-assessment and investigator-rated evaluations can be used in specific conditions. We also suggest that FDA consider discussion regarding adjustment strategy for conditions that may impact pubertal development (e.g., Turner syndrome, McCune-Albright syndrome, Kallman syndrome), that would be similar to what was provided for linear growth assessment
Lines 318-320	"Sexual maturity ratings should be based on both breast and pubic hair changes in females and on both genital and pubic hair changes in males. Evaluation of genital changes in males should include an assessment of testicular volume using an orchidometer." There are situations where such evaluation of genital changes may not be practical, either due to refusal of the child/teenager or because it requires a consult with an endocrinologist. It is also not necessarily the standard of clinical care depending on the situation and can be dependent on cultural concerns, introducing potential for unnecessary for psychological burden.	We suggest introducing flexibility around sexual maturity ratings.
Lines 331-367	Skeletal Age	IRBs may impose requirements on sponsors based on the draft guidance. We request that FDA provide more information around appropriate situations/indications where skeletal age measurements should be done. The addition of such language will help investigators and trial sponsors avoid unnecessary exposure to radiation for studies where measurement of skeletal age is not appropriate or will not offer

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		significant clinically meaningful information.
Lines 338-340	The guidance does not clarify that bone age assessments should be performed by suitably trained and experienced individuals.	We suggest including such language, e.g., "Bone age assessments should be performed by suitably trained and experienced individuals."

Conclusion

BIO appreciates this opportunity to submit comments regarding FDA's draft guidance for industry entitled "Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials". As FDA continues to consider revisions to the draft guidance, we would welcome future opportunities to discuss our recommendations.

Sincerely,

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