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October 28, 2022

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

Re: Docket No. FDA-2022-D-1562

E11A Pediatric Extrapolation; International Council for Harmonisation; Draft Guidance for Industry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Innovation Organization (BIO) welcomes the opportunity to comment on the Food and Drug Administration (FDA or Agency) draft guidance for industry entitled "E11A Pediatric Extrapolation".

We applaud the Agency's role in developing this important guideline as part of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and believe that alignment between global health authorities on the use of pediatric extrapolation during drug development will benefit industry and regulators alike, and ultimately, our 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.

In general, BIO appreciates that this guidance explains how pediatric extrapolation can be applied practically to support the safety and efficacy of a product in pediatric populations in a manner that will advance pediatric drug development globally. We also support the acknowledgement that extrapolation decision-making is complex, that knowledge evolves over time, and that gaps in information at the time of the initial pediatric development plan may be addressed during the execution phase of such a plan. Additionally, BIO believes the draft guidance provides sponsors with clarity on how to develop a pediatric extrapolation concept during drug development, including categorizing what is known, what is assumed, and what is a gap in information.

We are pleased to provide the following general comments regarding the use of pediatric extrapolation during drug development urge the Agency to consider our recommendations that we believe will further allow our members to bring safe and effective treatments to our pediatric patients more efficiently.

BIO acknowledges that the continuum approach discussed in Sections 1 and 3 of the guidance reflects that a continuum of dissimilarity/similarity may exist. However, despite this proposed continuum approach of assessing the disease similarity (as per Figure 1), the pediatric extrapolation plan in this figure seems to be still following the same concept of trichotomous categorization into full, partial, and no extrapolation. We recommend the addition of discussion on how this continuum approach would result in a potentially different pediatric development approach that follows a dichotomous decision tree. Providing more real-life or hypothetical examples to explain this continuity further would be helpful, whether in the guideline or in training materials.

We also recommend adding an overarching statement to encourage the sponsor to plan proactively with respect to inclusion of extrapolation the pediatric development program and streamline the endpoints in adults and children to address situations where the endpoint in adults cannot be reliably assessed in children.

In terms of applicability, BIO notes that it is not clear whether this guideline is intended to include vaccines. Similarly, we note that there are no considerations in the guideline for Companion Diagnostics (CDx) strategies in pediatric indications. Development of CDx in small pediatric indications can be challenging and regulatory guidance, e.g., as an Annex, in the training material, or in CDx-specific guidance, that provides flexibility would be helpful for situations where extrapolation may be used.

Next, BIO believes that a discussion regarding endpoint considerations and data presentations is also warranted. We recommend including details about situations when the biomarker cannot or was not measured in the reference population and the endpoint in the reference population cannot be measured in the target population. Similarly, we note that more information about extrapolation involving situations where populations are small or constrained, e.g., for a rare disease, would be helpful as a training example. In addition to what is presented, considerations for sample size calculation for pediatric rare diseases would be helpful in training materials. While using predictive distributions to establish similarity is not clearly discussed in the guidance, we believe this concept is critical for extrapolation to account for small sample sizes appropriately and should be included in more detail in the final guidance.

We further note that the current document does not include the “estimand” concept (ICH-E9-addendum) relative to reference or target populations. This concept is important when establishing the main questions of interest and the analytical methods tasked with answering them and believe it should be referenced in the final guidance.

Pediatric extrapolation is one of the core applications of FDA’s Model-Informed Drug Development (MIDD) Pilot, and BIO suggests inclusion of MIDD principles and thinking in training materials.

Regarding terminology, BIO recommends including a glossary of terms as the guidance uses or introduces terms with unclear meaning in the context of the guidance. For example:

- It is unclear whether “similarity of response” refers to the outcome under the experimental treatment, which is our recommended definition, or to the treatment effect relative to a control group, i.e., the difference between experimental treatment and a control.
- It is unclear whether “uncertainty” indicates “lack of precision” (due to small sample size) or to “questions about interpretation of a result”, i.e., potential bias.

- It is unclear whether “strength of evidence” (line 409) refers to “low uncertainty”, “absence of gap in knowledge”, or a different definition.
- In general, we recommend using the same term through the document to reference a specific concept instead of interchangeable terms, e.g., “reference population” and “source population”. Similar terms with different meanings should be defined clearly, e.g., “exposure response” and “PK/PD relationship” based on our understanding of the intended definitions.

In addition to the preceding comments, please consider the table outlining section-specific feedback on language in the draft guideline at the end of this document.

BIO appreciates this opportunity to submit comments regarding FDA’s draft guidance for industry entitled “E11A Pediatric Extrapolation”. As FDA continues to consider the harmonization of extrapolation practices relate to pediatric drug development globally, we would welcome future opportunities to discuss these points.

Sincerely,

/s/

Alex May, M.S.
Director, Science & Regulatory
Biotechnology Innovation Organization

SPECIFIC COMMENTS:

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Section 1.3 **Lines 45-48** **Section 3.5.1** **Lines 333, 342, 371** **Section 5.1** **Line 933** **(and elsewhere)**	The terminology "extrapolation of data" was first mentioned here and is included elsewhere in the document. This wording is misleading. The data itself can be analyzed or interpreted but not extrapolated. One is extrapolating the treatment effect, or the outcome measures, from a reference population to a target population (pediatric).	One recommendation is to replace, in this sentence and elsewhere in the document, "extrapolation of data" by "extrapolation of treatment effect" or "extrapolation of (safety/efficacy) outcome" or "extrapolation of findings".
Line 81 (Figure 1)	The graphic is useful to understand the spectrum, however the actual example is potentially oversimplified. At a first glance, the color coding would suggest that if there are differences in disease (red), and gaps in knowledge (red), then extrapolation is not possible (red).	Consider disconnecting the third arrow as this is related to the extrapolation plan (which can still allow/account for differences/gaps), rather than the extrapolation concept which is then represented by the 1st 2 arrows in Figure 1.
Line 81 (Figure 1)	The figure illustrating the continuum of evidence, the level of uncertainty, and the resulting impact they have on recommended studies in the plan to fill the gap is much appreciated.	However, we recommend adding a caption to clarify the message. An additional suggestion is to illustrate this in a 2-d graph. For instance, if the two main dimensions influencing the extrapolation plan are the similarity and the weight of evidence, those can be shown in a 2d graph (e.g., horizontal is the similarity, and vertical is weight of evidence). Thus, the extrapolation plan continuum would have multiple quadrants. Finally, it would be helpful to illustrate with a few examples how such graph could be used in submissions or in regulatory decision making.
Line 81 (Figure 1)	In case of having no markers that are predictive and relevant for clinical responses, and primary clinical endpoints are different between adult and pediatric trials, subcomponents common to both adult/pediatric primary clinical endpoints	Add "subcomponents common to both adult/pediatric clinical endpoints"

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	could be used (e.g., ACR20 vs ACR30 by Singh R.et al. 2021). Alternatively, the same secondary/exploratory endpoint could be used in E-R analysis to support efficacy extrapolation (e.g., CDAI in both Crohn disease ped and adult patients).	Add “same endpoints (secondary or exploratory)
Line 81 (Figure 1)	To this "high confidence end", it makes sense that exposure matching approach is included as it is the most abbreviated PSP. "Enrollment in or concurrent with adult trials” seems to indicate the scenario that a safety/efficacy trial needed in pediatric patients.	Move "Enrollment in or concurrent with adult trials” to under the “potential Study Designs/approaches"
Line 81 (Figure 1)	On the right side of the “Potential Study Design” image, “Enrollment in or concurrent with adult trials” as the study option may be misleading for high confidence in pediatric extrapolation. With high confidence in extrapolation, one could expect that a pediatric study could be omitted. In addition, if the effectiveness and safety have not yet been established in adults, it would be unethical to include pediatric patients.	We suggest providing alternative examples for the high confidence level in extrapolation for the “Potential Study Designs” image: e.g., omitting additional pediatric efficacy and/or safety studies. Or, if “Exposure matching” means omitting additional pediatric studies, we suggest clarifying.
II. PEDIATRIC EXTRAPOLATION FRAMEWORK		
Lines 86-87 Section 2	Revise for clarity: “The extrapolation framework consists of three parts: development of a pediatric extrapolation concept; and the creation and execution of a pediatric extrapolation plan (see Figure 2).” Due to use of current punctuation, it is not clear what the three parts are—as written, it appears to be two parts.	“The extrapolation framework consists of three parts: development of a pediatric extrapolation concept, the creation and the execution of a pediatric extrapolation plan (see Figure 2).”
Section 2 Line 107 Figure 2	Figure 2 (iterations as new information becomes available) suggests that going from extrapolation concept to extrapolation plan is an iterative process that is updated when new information becomes available.	However, how this iteration plays out is not mentioned in individual sections and it would be helpful to illustrate that with examples.
Section 2 Line 107 Figure 2	In most of the document, “data” refers to clinical data. However, information supporting disease similarity may rely on mechanistic models, published results, and some qualitative evaluations.	Thus, in this section of the graphic, we suggest being more inclusive of the source of information beyond clinical data, to avoid confusion. Additionally, we suggest replacing “synthesize available data” in this sentence with “synthesize

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		evidence" or "integrate relevant information".
Section 2 **Line 107** **Figure 2**	Within Figure 2, once an extrapolation plan is executed, there is only an arrow that points to 'data generated does not completely address knowledge gaps', therefore we suggest adding a note for when the gaps were solved, and extrapolation is completed.	It would be more accurate to include additional arrows out of the "Execution of Extrapolation Plan." For example, additional outcomes (arrow or arrows to pediatric authorization) may include: • omitting an additional pediatric study (no additional data needed), • conducting a more efficient pediatric bridging study, or • conducting a fully powered well controlled study. We also suggest the "Extrapolation Concept" include that any data and knowledge gathered in the successful execution of extrapolation feedback would inform future compounds in the same disease.
III. PEDIATRIC EXTRAPOLATION CONCEPT		
Section 3	The guideline lacks discussion on how a model could be built and validated on adult data, linking exposure and baseline risk factors to clinical outcomes.	We recommend expanding the explanation on using models for extrapolation in training materials.
Section 3	The guideline mentions that using the reference population to enrich the comparison in the target population assumes that there is sufficient similarity.	Whilst the guidance mentions that one should discuss this point in the extrapolation concept, BIO requests additional guidance on how to assess similarity between reference and target populations through training materials.
Section 3	The guideline provides overlapping considerations across the three cornerstones for the assessment of extrapolation.	We recommend that training materials should provide a case example on what differential assessment is needed in each section (e.g., similarities, mechanism of

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		action, response to treatment).
Section 3	We note that this section refers to the pediatric population in general and does not account for potential age differences.	We suggest clarification that assessments should be completed separately for each pediatric age group.
Lines 120-376	The guideline discusses the importance of several factors that should be considered to develop a pediatric extrapolation concept. However, further clarity on how the factors should be prioritized and what a good assessment would like would be beneficial.	We recommend that training materials should include case examples in different therapeutic areas (e.g., Oncology, general medicine) to show how factors can be identified and demonstrate what a good assessment of similarity may look like.
Line 120 Section 3	"All the relevant populations."	Replace with "Both the reference and target population".
Lines 122-216 (Section 3.1 "Disease Similarity")	Disease similarity is independent of the drug being developed. Examples are provided in the guidance for infectious diseases and seizures; please include other diseases as well (e.g. polyarticular course juvenile arthritis vs. adult RA; pediatric and adult autoimmune diseases (atopic dermatitis, Crohn's disease, and ulcerative colitis).	Please include a list of pediatric diseases which are considered as adequately similar to adult diseases based on current evidence to support extrapolation in training materials.
Lines 151-161	For oncology, it is important to mention genotypic expression or tumor specific mutations as it is a very important factor for similarity/unsimilarity.	We recommend the following edits: "Evaluation can also include a determination about whether differences in the clinical presentation of disease may depend upon the age of onset, age-dependent phenotypic expression, genotypic expression, tumor-specific mutations, or other age-related differences."
Section 3.1.1 Line 177	Add prognostic and predictive factors instead of just factors.	Are there other prognostic and predictive factors to consider …?
Section 3.1.1 Line 192-194	It seems difficult to understand the sentence "What effect have these treatments (e.g., timing of treatment relative to onset of disease and age of the patient, frequency of treatment, length of treatment) had on the course of the disease in the reference and target populations?"	Clarifying edits: Are there similarities or differences in these treatments (e.g., timing of treatment relative to onset of disease and age of the patient, frequency of treatment, length of treatment)

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		and what effect have they had on the course of the disease in the reference and target populations?
Section 3.2	BIO notes that a discussion regarding what absorption, distribution, metabolism, and excretion (ADME) characteristics for new modalities (e.g., gene therapy) where traditional ADME properties are not applicable, would be helpful. Moreover, while immunogenicity is part of safety, it is also part of mechanism of action (MOA), factors affecting pharmacokinetic/pharmacodynamic (PK/PD), and response.	Additional explanation of these concepts would be helpful through training materials.
Section 3.2 **Lines 219-221**	"In addition, differences in MOA properties can result in differences in an exposure-response relationship between the reference and the target population..." The consequences of such differences in exposure-response between reference and target population for the extrapolation concept are unclear.	Please discuss in training materials.
Section 3.3	We recommend that FDA considers adding discussion about situations where similarity of response in pediatric patients and adults is established in another disease for the same drug.	For example, we suggest training materials about the objective criteria to use for such similarity in other indications to inform possible similarity of response to treatment in the new indication between adults and pediatric patients, which endpoint should be used to assess this similarity (e.g., PD biomarker), and potential solutions for situations where the response endpoint is not the same between both indications.
Section 3.3	In this section (and elsewhere in the guidance) the terms "PK/PD relationship" and "exposure-response relationship" are being used.	It is not clear whether these terms are to be understood as synonyms, in which case only one of the two terms should be used throughout the document, or if they describe two slightly different concepts, in which case a definition of the two terms would help.
Section 3.3	It is not clear whether the term "similar response to treatment" refers to the	This should be clarified, and these two aspects should be

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	treatment under investigation, or whether it refers to all treatments in general.	dealt with separately. Much of the content of the section (for example when discussing endpoints) seems to refer to treatment in general. Similarity of the response to the treatment under investigation is somewhat limited here to similarity of exposure-response and fits better in Section 2.
Section 3.3 Lines 225-229	"...response to treatment..." and "response to the drug, other drugs in the same class and in other classes." We agree that similarity of response to treatment is important but that not only includes the test treatment but also the comparator/control because the treatment effect is usually a contrast between response to a test treatment versus response to control (most often placebo).	Thus, we suggest adding "response to treatments (test and control)" and "response to the drug, the control, ..."
Line 228 Section 3	"(parent and/or metabolite(s))"	Change to "(parent and/or active metabolite(s))"
Section 3.3 Line 229-231	Recommend expanding on the sentence "Similarly, data generated in other indications for the drug can serve as a relevant source of knowledge when assessing the similarity or difference of response to treatment" by adding text regarding the mechanism of action.	Similarly, with respect to the mechanism of action, data generated in other indications for the drug can serve as a relevant source of knowledge when assessing the similarity or difference of response to treatment.
Section 3.3 Lines 231-233	This statement seems to imply that the assumption of similar exposure-response is required. In many indications a proper dose finding study cannot even be done in adults, so that our knowledge about the adult exposure-response is limited (case 1). In other indications, we may have an adult exposure-response, but we can only collect limited data in children (by using just one pediatric dose regimen that matches the exposure observed under the registered adult dose regimen (case 2)). The case where we can assess similarity of exposure-response with adequately characterized E-R relationships in both populations (case 3) is probably rare.	This would be helpful to include in training materials, as it is important for the pediatric dose selection (which is usually a dose that achieves the same exposure as observed in adults when treated with the registered adult dose). Also, the training materials should discuss in more detail how to handle different cases.

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Section 3.3.1	BIO notes that a discussion regarding how the correlation between endpoints can be established and what are acceptable data and criteria to establish this correlation would be helpful. Additionally, we recommend that the final guidance describes alternative solutions for situations where the correlation between endpoints cannot be established. In some diseases, the minimum clinically important difference (MCID) in pediatric patients might not be well understood and could differ from adults.	Guidance on how response might be extrapolated in these situations would be helpful.
Lines 236-245	It would be useful to clarify if this section related to 'therapeutic' response (i.e. efficacy) as oppose to an overall response, which can encompass both efficacy and safety.	As with similarity of disease, the similarities, and differences in therapeutic response to treatment between a reference and target population should be understood as a continuum. To assess similarities and differences of therapeutic response to treatment, a thorough review of available knowledge in both the reference and target populations should be conducted, including the therapeutic response to the drug, other drugs in the same class and in other classes. Similarly, data generated in other indications for the drug can serve as a relevant source of knowledge when assessing the similarity or difference of therapeutic response to treatment.
Section 3.3.1 **Lines 241-249**	The current section implies that PK/PD must be done in a single step, however we often establish a PK model in one step and then a PD model in a second rather than doing a single joint PK/PD analysis. The text suggests that only a single joint PK/PD analysis is intended, but that is not easy to do in many instances.	Please consider expanding the language to include 2-step procedures.
Section 3.3.1 **Lines 251-259**	Currently, the document only lists the questions without providing any guidance.	Please provide additional guidance explaining why these questions are crucial to consider when evaluating the

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		similarity of response to the endpoint(s) and discuss the consequences that might result from different possible answers. We also suggest adding a note that these are not the only type of questions that Sponsors should evaluate but rather a recommendation.
Lines 253-262 ("Pharmacokinetics and pharmacodynamics [PK/PD]" section)_	There are cases where prior treatments might be different between adults and pediatrics which in turn might result in different drug/safety and drug/efficacy relationships between the two populations based on previous therapies received.	Please modify the guidance to include that one additional aspect sponsors may need to consider is the treatment landscape for the disease between adults and pediatrics.
Lines 263-283, Section 3.3.1	Another question that can be considered under Response endpoint(s) would be the different distribution of risk factors between reference and target population, which make the response "different". For certain inherited diseases, patients who live long to become an adult often have less severe type of disease. As a result, a larger portion of pediatric patients have more severe type of disease and thus respond to treatment less robust than adult patients.	Suggest adding a bullet as below: "Are there different distribution in risk/prognostic factors impacting the response between target and reference population"?
Section 3.3.1 Lines 261-267	Please include language about the impact of effect modification of some characteristics (e.g., by age, and weight) on the evaluation of similarity.	For example, if in the reference population, the magnitude or direction of the treatment effect (contrast between test and control) varies by age or weight, then these factors interact with treatment on response in the reference population. It would be helpful to clarify the impact of such interaction on the extrapolation plan to the target pediatric population.
Section 3.4	The guideline lacks examples for situations where nonclinical data become relevant due to feasibility reasons. For example, the endpoint or PD biomarker cannot be measured in pediatric patients (e.g., due to complexity in sampling or inability).	We suggest adding examples on this topic.

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Lines 277-283, Section 3.3.1	It would be helpful if discussion around selection of clinical responses in scenarios that pediatric and adult clinical studies have different clinical response measurement for primary endpoint, in such case, common subcomponents or secondary endpoints could be used in the expose-response analysis.	If not included in line 83, it would be helpful that a discussion around similar clinical endpoints regardless of order of objectives in pediatric or adult trial could be used or subcomponents common to clinical endpoints in pediatric and adult could be also mentioned here.
Line 278, Section 3.3.1	Along with age/maturity, body weight can play a major role as well, therefore it should be considered.	Consider rephrasing "Age/ maturity-related factors" to "Age/ maturity-related (e.g., body weight) factors".
Section 3.4 Line 281-283	Table 1 should list or mention some other possible "private or publicly available databases" (e.g., NHANES)	Add to the section entitled “Other sources” the following text: “Private or publicly available databases (e.g., NHANES)”
Section 3.4 Lines 281-284 Table 1	Although the table lists the sources, not the motivation for data collection, and IIT & off-label data should be captured in various types of data sources, IIT/off-label data and the results from published papers are not explicitly mentioned within the guidance.	This is a crucial data point, and it would be beneficial to explicitly state that these are acceptable data sources.
Section 3.4 Lines 281-284 Table 1	Table 1: Clinical Data; second row: “PK, PK/PD, E-R, and clinical data in other **related** conditions for a drug or drugs in the same class”	Please clarify the meaning of “related” and whether it refers to conditions within a category such as immune diseases e.g., psoriasis, JIA, SLE, MS, etc. It would also be helpful to understand how much information could be leveraged, e.g., only PK/PD data versus other types, as well as whether it could be used for dose, safety, and/or efficacy.
Lines 286-288	"Clinical data (e.g., from controlled trials, prospective observational studies, PK, PK/PD and/or biomarker studies) in populations with the same condition or related conditions should be evaluated to understand similarities and differences between the reference and target populations."	We propose the following addition: "Clinical data (e.g., from controlled trials, prospective observational studies, PK, PK/PD and/or biomarker studies, tumor banks with

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	Tumor banks with assessment of relevant biomarkers should be included in the text.	assessment of relevant biomarkers) in populations with the same condition or related conditions should be evaluated to understand similarities and differences between the reference and target populations."
298, Table 1: Examples of Sources and Types of Data to Evaluate for Similarity of Disease and Response to Treatment	Row: "Clinical Data" This section may benefit from combining the sub-rows under "Types of Data" as it is clearer to list the same disease condition for both the same class and a different class.	We suggest combining the first and third sub-rows under "Types of Data" to one row to simply the Table.
Section 3.5	We note that it may be helpful to also include considerations regarding the extrapolation of immunogenicity for biologics.	Please consider expanding the guideline to include this topic.
Lines 339-344	It would be useful to clarify if for the purposes of safety extrapolation the similarities and differences of the safety profile between the reference and target population can be considered as a continuum similarly to the treatment response.	Similarities, and differences in the safety profile between a reference and target population should be understood as a continuum.
Section 3.5.1 Lines 346-348	The text currently limits inclusion to adolescents. Consider adding additional text that could facilitate an understanding when even broader inclusion to children could be considered appropriate.	Please include children within this paragraph as pediatrics does not include only adolescents. "Enrollment of adolescents and children in/or concurrent with the adult trials may..." Another option would be adding a note that the term 'adolescents' as it's used within this guidance covers all age cohorts (i.e., neonates, infants, children, and adolescents).
Lines 348-355	"Extrapolation of safety data could be considered based on the available knowledge of the known and/or potential safety issues in the reference population that are relevant to the target pediatric population. Other information (e.g., nonclinical, mechanistic) should be considered as part of this analysis. These	With respect to vaccines, this approach could apply; however, there are always uncertainties regarding the rare adverse events following vaccination like intussusception and rotavirus vaccine, febrile convulsions

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	data should help increase certainty about the expected safety profile of a drug in a particular pediatric population and determine if additional gaps in knowledge need to be addressed in the pediatric program."	and MMRV, etc. Therefore, clinical trials to evaluate the vaccine's safety in the pediatric population could not be completely replaced by safety studies in the adult population. The main issue with vaccines is the coincidental events that can undermine the public health trust in vaccination programs if not assessed during clinical development.
Lines 366-393	(List of questions to be reviewed when considering extrapolation of safety)	Please modify the guidance to make it clear as to whether all the mentioned considerations need to be met for safety extrapolation to be considered acceptable.
3.5 Safety Considerations in the Extrapolation Concept	It is helpful and relevant to know how much of the data that has been generated in the reference population could be used to improve the interpretability of the safety data in the target population.	The Guideline uses “a priori” information for efficacy evaluation and extrapolation. We suggest adding similar language to Section 3.5.1. Extrapolation of Safety for methods that use a priori for safety evaluation.
Section 3.5.1 Line 372	Please explain these “circumstances” in more detail, beyond there having to be confidence.	Please elaborate further on this example
Section 3.5.2 Lines 380-383	A reader who is not familiar with this specific situation may not understand why and how “the effect of corticosteroids on reduction in growth velocity” is a good example for the need to collect additional safety data.	Please elaborate further on this example in training materials.
Lines 380-381	We suggest deleting the following sentence as it doesn’t seem to be relevant to safety extrapolation: How does the expected treatment duration and treatment effect size in the reference population compare with the target pediatric population?	Delete following sentence: How does the expected treatment duration and treatment effect size in the reference population compare with the target pediatric population?
Lines 383-385	We suggest adding recommendation for conducting an exposure - AE relationship as an example of determining if the exposure needed to target an specific PD effect or clinical response predict a specific toxicity in the target population	Does the exposure needed to target a specific PD effect or clinical response predict a specific toxicity in the target pediatric population as determined by for example

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		any relationship between exposure and frequency and severity of any specific adverse events?
Section 3.5.2 Line 386	Please explain the "special considerations" for the four cases in more detail.	Please elaborate further on this example in training materials.
Line 393	We suggest adding a specific question around whether there is a known PK safety relationship with the drug in question. It will be easier to fill in safety data gaps using extrapolation with drugs that have a wide therapeutic index, i.e., no known PK safety relationship.	Does the drug have a known PK exposure safety relationship? Has this been explored with modelling?
Section 3.5.2 Lines 394-397	Please elaborate how study designs might depend on the gaps, ideally with an example. It is unclear what is considered an arbitrary sample size and what is an appropriate scientific justification of sample size. It is also unclear whether a sample size that is based on incidence and prevalence rates (and hence the ability to recruit) is arbitrary.	Consider providing an example or more elaboration in training materials around the exposure matching scenario to clarify how sample size/duration is expected for safety bridging.
Section 3.6 Line 421-450	This section focuses on integrating evidence around the endpoint without much discussion about heterogeneity assessments of the populations that are essential in any evidence integration.	Please include guidance on evaluation of heterogeneity of population and findings in the reference population.
Line 422	For some diseases, the pediatric extrapolation concept has already been established. For example, partial onset seizures, antibacterials, and antivirals. It would be duplicative and inefficient for each pediatric program to redo the evidence synthesis in such cases.	We suggest including that in some diseases, pediatric extrapolation may already be well-established.
Section 3.6 Lines 426-427	Please revise the sentence to include safety.	"Meta-analytic techniques for synthesizing efficacy and safety data in the reference population(s) should also be considered."
Section 3.6 Lines 430-431	"The most appropriate method will depend upon the parameters being evaluated for similarity assessment."	Please elaborate the intent behind this statement.
Section 3.6 Starting line 431	We suggest including considerations around variability in the population, prognostic & predictive factors. As well as *predictive* comparisons.	

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Section 3.6 Line 431	Evaluation of similarity can go beyond parametric modelling. Thus, using parameters in this sentence can restrict methodologies of integrating evidence and exclude machine learning methods or non-parametric methods of integrating evidence. We suggest replacing "parameters" with "factors" or "considerations" or "endpoints".	It would be helpful if the guidance would include a glossary of terms, all technical terms should be defined, and then used in a harmonized manner throughout this document.
Section 3.6 Lines 433-438	This text transitions rapidly from confidence intervals to a model.	Please elaborate on what modeling the guidance is discussing here. What is appropriate if overlapping of confidence intervals are inappropriate?
Section 3.6 Lines 447-450	The meaning of "uncertainties in the data" is unclear. It could be interpreted to mean that in the vast majority of the cases, at time of defining extrapolation concept, there is no response data for the investigational drug in the target population/indication, and thus assessment of similarity involves untestable assumptions.	Please clarify.
Section 3.6 Lines 460-461	Please include recommendations about when the extrapolation concept can be finalized, in spite of remaining gaps.	Please clarify and/or add examples.
IV. PEDIATRIC EXTRAPOLATION PLAN		
Section 4.1	This section should also consider include situations where the baseline prognostic factors may not be the same between adults and pediatric patients. Additionally, ICH experts may consider expanding on the situation where tissue PK/PD is important and when data are needed for metabolite/anabolite PK/PD data collection.	
Section 4.1	There is no mention of how PK extrapolation could play a role in pediatric exposure-matching.	We suggest including language in the guideline on pediatric exposure matching and how it could be achieved by either a dedicated study, or by extrapolation using modeling and simulation without a dedicated pediatric PK study when the confidence in pediatric PK prediction is high.
Section 4.1 Lines 505-510	Phrasing	Please delete the word 'However," and simply start the sentence with "The lack of..." or to simplify the

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		sentence, we suggest restating to read, “Exposure-matching may still be utilized in the absence of demonstrable E-R relationships when the expectation that a comparable response at the target drug exposure is likely to be achieved”.
Lines 507-510	"Dose selection based on exposure matching under such circumstances is reasonable and pragmatic and is predicated on the expectation that comparable response at the target drug response is likely to be achieved." This sentence should be modified as it does not make sense in the context of exposure matching.	We propose the following edits: "Dose selection based on exposure matching under such circumstances is reasonable and pragmatic and is predicated on the expectation that comparable response at the target drug ~~response~~ exposure is likely to be achieved."
Section 4.1 **Line 509**	The meaning of “comparable response at the target drug response” is unclear.	Consider an alternative: “... expectation that comparable response is likely to be achieved at similar drug exposure”?
Lines 513-519, **Section 4**	As part of the pediatric extrapolation plan, it is unclear whether a sponsor should highlight somewhere that the design of these pediatric studies should be kept consistent with the corresponding adult studies. In doing so, a confirmatory understanding on disease/response similarities can be established.	Please clarify
Section 4.1 **Lines 514-526**	Please define what is meant by “confirmatory PK” here.	
Section 4.1 **Lines 519-522**	Please elaborate on why sponsors cannot use PK information obtained from an efficacy/safety conducted in the target pediatric population here.	For example, in case of “differences in the effect of PK of the drug between reference and target population”, it is unclear whether exposure-matching is still a good objective?
Section 4.1 **Lines 522-526**	The reference pediatric population with a difference disease and target population should generally be with same age range, (e.g., both populations are 1~5 years old). Otherwise, it is not applicable to believe that	Suggestion: “Lastly, additional PK data in the target pediatric population may not be required if there are PK data on the experimental drug from

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	PK assessments are unnecessary. Please revise the sentence to reflect this.	a different pediatric population / indication. This data should usually include the same age range as relevant for the target pediatric indication. However, this approach relies on understanding the effect of disease on the PK of the drug."
Lines 523-528, Section 4.1	In the paragraph "before initiating pediatric studies", consider adding the prior existence of adult clinical data as key consideration before planning a pediatric study.	
Lines 527-528, Section 4.1	Clinical endpoint differences but could be used for extrapolation (JIA vs RA)	Add difference in clinical endpoint.
Lines 534-536, Section 4.1	"It is important to note that the identification of safe and effective dose(s) in the program with the reference population does not always require or result in the demonstration of an exposure-response (E-R) curve. As such, there is no requirement to establish an E-R curve in pediatrics."	Consider clarifying or providing guidance on when E-R curve would be required and when it would or would not be helpful (an example might suffice).
Lines 537-539, Section 4.1	"However, the lack of demonstrable E-R relationship in the reference population or the inability to demonstrate similar E-R curves in the reference and target populations does not preclude the use of exposure matching for dose selection purposes in the pediatric extrapolation plan." It is unclear when exposure matching would be appropriate when E-R relationships are not known/demonstrated.	Consider providing an example in training materials as to when exposure matching would be appropriate when E-R relationship are not know/demonstrated.
Section 4.1.2	BIO requests that the final guidance includes an example for a situation where a biomarker can be measured in pediatric patients but not in adults and is used as the primary endpoint for pediatric patients	
Lines 545-557	Confirming PK as part of pediatric efficacy/safety studies with the use of sparse PK carries the risk of potentially finding out that PK is different only after the study has been concluded, possibly resulting in a failed study due to unfavorable efficacy/safety since the doses evaluated do not achieve the target optimal exposures.	If this approach (i.e., confirming PK as part of pediatric efficacy/safety studies with the use of sparse PK) is to be pursued, please modify the guidance to recommend assessing PK (through serial sampling if possible) in an early PK run-in cohort within the efficacy/safety study. This approach provides room for

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		dose adjustments to be implemented early in the study if PK is found to be different than expected.
Lines 547-548, Section 4.1	In some cases, such as Fixed dosed combinations, it is unclear whether it can be considered acceptable if there is PK available in pediatrics for only one drug from prior studies and there is no combination effect on PK of either drug from adult data.	Please clarify
Lines 550-552, Section 4.1	In these cases, if the concern is mainly about safety, the study can be a separate PK/safety study, rather than a dedicated PK study. In these cases, the exposure matching approach can still be used to define a potential dose as a starting point for further evaluation with up or down dose modifications.	Change “a separate PK study” to “a separate PK/safety study”.
Lines 552-555	"If a biomarker has been proposed for use as a primary analysis in the target population and cannot be measured in the reference population, relevant clinical outcomes in the target population should at least be measured as well, to try and understand the relationship between the variables." The term "variables" is unclear in this sentence.	We recommend the following edit for clarity: "If a biomarker has been proposed for use as a primary analysis in the target population and cannot be measured in the reference population, relevant clinical outcomes in the target population should at least be measured as well, to try and understand the relationship between the ~~variables~~ biomarker and clinical outcomes."
Lines 553-557, Section 4.1	In some cases, when the safety margin is wide, it may be acceptable to target slightly higher exposures in adolescents/pediatrics compared to adults with the same flat dose (E.g., With the same adult flat dose in adolescents, the exposures in low body weight subjects can be higher than reference median adult exposures with the same dose. However, if the safety is established in adults at much higher dose levels, it can be considered acceptable to have the same adult recommended dose in adolescents in some cases.)	In cases when there is a wide safety margin, the acceptability of targeting slightly higher exposures in adolescents/pediatrics compared to adults with the same adult recommended flat dose needs to be justified.
Section 4.1.3.1	BIO suggests providing more clarity for situations where PK data may not be needed	

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	and a complete reliance on model prediction is allowed, even in the absence of PK data in another pediatric reference population.	
Section 4.1.3.1 Lines 559-574	Please consider situations where the outcome of the study is negative, i.e., exposure in the target population does not match that in the reference population. It is unclear whether sponsors should redo a new PK study or if it is acceptable to determine the pediatric regimen by modelling and simulation based on this “failed” pediatric study.	If the latter is possible, it should be mentioned in the guidance.
Section 4.1.3.1 Lines 562-574	Please clearly define the dosing strategy based on exposure matching.	Please specific whether it always consists of selecting a pediatric regimen that achieves an exposure in the target population similar in mean and distribution to that in the reference population treated with the approved regimen. It would be helpful to clarify any exceptions to this rule, e.g., if the adult bodyweight extends beyond the pediatric bodyweight significantly, the matching exposure strategy may result in pediatric patients receiving a lower dose compared to adults of the same bodyweight.
Lines 564-566	"Modeling and simulation strategies should be applied to support the initial dose selection in the exposure matching study in the target population (see section 4.2)." Please define 'exposure-matching study' and clarify if it means a Phase 1 single-dose study, or can other Phase 2/3 studies provide this information.	The guideline should define 'exposure-matching study' and clarify whether it means a phase 1 single-dose study or if other phase 2/3 studies can provide the necessary information.
Section 4.1.3.1 Lines 576-589	It is unclear whether it is necessary to design a PK study in the target population allowing sponsors to evaluate the steady state PK metric or if it could be acceptable to characterize the PK based on a single dose study (and extrapolate the steady state PK metric based on modelling).	If this is possible, it should be mentioned in the guidance.
Lines 577-579	"When the pediatric extrapolation strategy relies on matching adult exposures, the	Please consider the revisions below.

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	target exposure metric(s), range, and acceptance criteria should be prospectively specified and should be defined in the context of the disease, treatment regimen, route of administration, and formulation." It would be difficult to pre-emptively specify a criteria for an 'acceptable' exposure range, as subsequent pediatric studies might demonstrate a slightly different exposure-response relationship than that observed in the reference population, which would result in evaluation/approval of a slightly different exposure range and therefore, dose regimen.	"When the pediatric extrapolation strategy relies on matching adult exposures, the target exposure metric(s), range, and acceptance criteria ~~should~~ may be prospectively specified, if applicable and should be defined in the context of the disease, treatment regimen, route of administration, and formulation."
Line 590, Section 4.1.3.1	It is unclear whether there is a scenario when only PK data are needed to establish safety	If there is no such scenario, we suggest clarifying somewhere in the guideline.
Section 4.1.3.1 Line 591-607	The 'criterion for success' is imprecisely defined in the two sections. It is understandable that defining such a criterion is not simple as it depends on many aspects, including feasibility, and width of therapeutic range. Still, it is important to define it clearly and concisely in the sample size section. The principles driving the sample size evaluations are unclear, e.g., the hypotheses or the estimands of interest. It is unclear what it means to derive a sample size to fill a knowledge gap, i.e., evaluating feasibility resources rather than study power or precision.	Please consider revising this section so that the objectives of a pediatric PK study are clearly stated and guided by practical considerations. Usually this would be to demonstrate that the initial pediatric dose matches the exposure observed in the reference population. This can be demonstrated graphically (see example graph from EMA) by providing the adult reference range and by plotting the observed pediatric exposures against this. If weight-based dosing (say) was used, weight can be plotted on the x-axis against the exposure-metric on the y-axis. Predicted exposure range in the target population (by weight) as obtained from the original model can also be added. A sample size (potentially per age group) should be based on practical considerations like incidence of the disease. For a more formal sample size calculation

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		(whether by statistical or modeling and simulation approaches) one would need to define a more formal criterion. In principle, this could be some sort of equivalence test against adult reference data or a model-based prediction, but such approaches have issues of their own.
Lines 592-593	"The sample size for a pediatric PK study should be sufficient to meet the objectives of the study and be based on quantitative methods (modeling and simulation and/or statistical approaches)." This sentence should be revised since quantitative methods may not always apply. Most PK studies are conducted with a sample size selected based on feasibility, for purposes if empirical comparisons also supporting population PK/PD analyses, and ethical considerations.	"The sample size for a pediatric PK study should be sufficient to meet the objectives of the study and may be based on quantitative methods (modeling and simulation and/or statistical approaches), as appropriate"
Section 4.1.3.1 **Lines 594-595**	Simply stating that Sponsors should have adequate representation is not enough information.	The guidance should provide further elements of rationale.
Section 4.1.3.1 **Lines 598-599**	Parameters like clearance and volume are determined based on a popPK model. This popPK model will usually be based on a pooled data set which may include adult patients and patients from other diseases treated with the same drug. The sample size for such a popPK model should be seen as a separate problem to the sample size for a pediatric PK study to demonstrate exposure matching.	The guidance should make this clearer to the reader.
Lines 606, 626	Model-informed dose selection feasibility and practicality of dosing strategies as well as the sample size feasibility is mentioned but the guideline does not include further details on the feasibility. There is currently limited information or guidance in this document for when there are situations or programs where there is lack of prior data available, lack of validated pediatric endpoints or sample sizes, and circumstances when efficacy studies are not required.	It would be beneficial if the feasibility topic briefly mentioned in the guideline was expanded through training materials. Additional guidance and recommendations regarding feasibility in general for pediatric studies as well as the special situations mentioned (lack of prior data, lack of pediatric validated

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		endpoints, etc.) would be helpful to include in these training materials when developing pediatric programs.
Section 4.1.3.1 Lines 609-634	Within this subsection, there are some statements which recommend using simple methods like confidence intervals or graphical procedures, and other statements where model-based approaches are recommended.	Please include a discussion under which circumstances to use the simpler approach, and under which circumstances to use a model-based approach. What is also missing is a high-level description of how such a model-based approach could look.
Lines 609-616	"*Analysis and reporting* Different presentations of the exposure data in the target and reference populations should be available to inform regulatory decision making. A single acceptance boundary for all drug products and drug classes (as compared to bioequivalence testing) will not provide a meaningful approach in the setting of pediatric extrapolation. An evaluation of confidence intervals for the mean differences in key exposure metrics such as AUC and Cmax could be an acceptable approach. The chosen boundaries of the confidence interval should reflect the context of the therapeutic range of the drug and the risk-benefit of the product for a given pediatric indication." This section should also note that there may be many instances where exact exposure-matching is not warranted for selection of the most appropriate pediatric dosage, such as when target expression in pediatrics can differ, or when the dose can be selected primarily from PD response matching instead.	We propose the following edits: "*Analysis and reporting* Different presentations of the exposure data in the target and reference populations should be available to inform regulatory decision making. A single acceptance boundary for all drug products and drug classes (as compared to bioequivalence testing) will not provide a meaningful approach in the setting of pediatric extrapolation. An evaluation of confidence intervals for the mean differences in key exposure metrics such as AUC and Cmax could be an acceptable approach. The chosen boundaries of the confidence interval should reflect the context of the therapeutic range of the drug and the risk-benefit of the product for a given pediatric indication. However, there may be many instances where exact exposure-matching is not warranted for selection of the most appropriate pediatric dosage, such as when target expression in pediatrics can differ, or when the dose can

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		be selected primarily from PD response matching instead."
Section 4.1.3.1 Lines 615-616	It is unclear whether this sentence is referring to the threshold (e.g., 0.8, 1.25) or the significance level of the confidence interval.	Please clarify as the latter could be informed by the risk benefit but not by the therapeutic range, and vice-versa for the former.
Section 4.1.3.1 Lines 618-619	A direct comparison of observed exposure data in reference and target population by graphical means is preferrable because it does not rely on any assumptions.	Suggest changing preference and to explain when model-based comparisons might be preferrable over direct ones.
Lines 621-623	"A simulation of the percent of subjects at different age/weight ranges that lie within (or outside) a pre-defined exposure range may provide a more meaningful assessment of exposure similarity." It would be difficult to pre-emptively specify a criteria for an 'acceptable' exposure range, as subsequent pediatric studies might demonstrate a slightly different exposure-response relationship than that observed in the reference population, which would result in evaluation/approval of a slightly different exposure range and therefore, dose regimen.	We propose the following edits: "A simulation of the percent of subjects at different age/weight ranges that lie within (or outside) a ~~pre-defined~~ target exposure range may provide a more meaningful assessment of exposure similarity."
Lines 622-643, Section 4.1.3.1	In some cases, it may be difficult to enroll the desired number of patients across age ranges due to the rarity of the disease, enrollment and operational challenges. It is unclear whether it would be possible to use pediatric data from other indications. Also, it may be difficult to assess food effect/formulation effects etc. with lower sample size when this has already been established in other studies such as adults etc. for small molecules. In such cases, the reasons for studying smaller sample size in pediatrics (eg. with a newer formulation) and the proposed sample size should be justified.	Suggest adding one sentence at line# 638 or line# 643: In circumstances where it is difficult to enroll desired number of patients (eg. rarity of the indication, challenges in enrollment), the availability or feasibility and adequacy of using PK data from other pediatric indications should be considered and justified.
Section 4.1.3.1 Lines 629-630	In some cases, it would be better to treat age and BW as use category covariates.	Please delete “on a continuous scale”.
Section 4.1.3.2 Lines 636-652	In principle there are two ways how biomarkers can be used. One could use an exposure-biomarker relationship for extrapolation (i.e., the biomarker replaces the response), or one could use a biomarker	

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	matching strategy (i.e., the biomarker replaces exposure, and one needs to find a pediatric dose that matches the biomarker levels observed in the reference population). These different approaches should be discussed in more detail.	
Section 4.1.3.2 Line 639	Clarify the meaning of “validated biomarker” (vs. “qualified biomarker, for example).	Consider including a definition or clarification of the meaning of "validated biomarker."
Lines 644-652, Section 4.1.3.1	It is unclear whether this approach would be acceptable for clinical response comparison	It would be helpful to outline what is generally acceptable to demonstrate similarity in clinical response
Section 4.1.3.2 Lines 670-672	Please elaborate why in this case of biomarker, it is necessary to confirm the established DER relationship, while for clinical endpoint, it is not necessary to establish DER relationship (line 504).	
Section 4.2 Line 706-712	The intent of this section is unclear	The section would benefit from the addition of references. Also, please consider expanding on the considerations/acceptability of using pooled datasets or Bayesian approaches with prior distributions.
Section 4.2 Lines 719-721	Assumption testing is an important aspect that should be considered	Please elaborate further on how to do this, rather than simply stating that one needs to do this.
Section 4.2 Lines 725-734	It is important to distinguish between variability (between-subject) that naturally exists in the population and modelling or measurement error uncertainty that is model or instrument specific.	Please clarify this distinction
Line 737-741	This section on Clinical study only references the use of control arm using external information. Another way to leverage external information, for both on control and treatment arm, say from adult program in the same compound (using Bayesian framework) in situation where the standalone pediatrics study is small and not fully powered for statistical significance on its own. This of course will depend on the demonstration of no expected different treatment effect in pediatric population than that from adults like all other situations. Such scenarios are not clearly mentioned in the	Some discussion (or at least acknowledgment) of additional scenario would be helpful.

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	guidance though one of the FDA reviews of the Lupus pediatric study utilized such technique, refer FDA Review 2018: https://www.fda.gov/media/127912/download (Pages 99 onwards).	
Section 4.3.1. Lines 743-753	We agree that single arm studies may be the most appropriate design when running a pediatric efficacy trial under an extrapolation approach. However, the justification (standard of evidence in the reference population being a single arm trial) should be further explained. There are other more important reasons why to conduct a single arm trial. For example, a registered control for children may not exist, and a placebo control may be unethical. As another example, lack of ability to recruit may be a reason for running single arm trials in pediatrics. This may even be the case in non-rare pediatric indications, because there may be too many pediatric studies ongoing in one indication at the same time, or because there is already a registered good treatment option and parents may be reluctant to consent to a clinical trial.	Please provide additional explanation of the justification
Section 4.3.1 Lines 749	This discussion of threshold is unclear.	Please clarify how the threshold will be establish or justified, as well as the meaning of "sufficient precision"
Section 4.3.2	We note that it is important to clarify the regulatory expectations as well as the situations where the use of external data is successful and when it is not.	ICH experts may also consider referencing other guidances on this topic.
Section 4.3.3 Lines 774-776	This part of the section is unclear	Please clarify whether this section is restricted to dichotomous endpoints and what are considered false positive and false negative in the context of concurrent controls.
Section 4.3.3 Lines 781-782	"The extrapolation approach will result in a sample size smaller than one would expect for a standalone efficacy study." This may be true sometimes but may not always be true. Sample size reduction depends on the knowledge gap, uncertainties in the extrapolation, and the	Thus, we suggest adding qualifying statements. "The extrapolation approach may reduce the sample size needed to fill the knowledge gap relative to using a standalone efficacy study."

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	study design being considered for the standalone study. Also, if the extrapolation assumptions do not hold, then there will be a bias and will lead to more studies/additional sample size.	
Section 4.3.3 Line 787	The meaning of “consistency” is unclear in this context	Please clarify the meaning of “widen the non-inferiority margin” in this context
Section 4.3.5 Lines 808-816	It is unclear whether this paragraph refers to a specific situation, where Bayesian analysis with informative priors is being used.	Please provide the context in which this paragraph applies.
Line 818-819	Guidance mentions 'mixture prior' or 'power prior' as part of the Bayesian methods, but it is not clear why it did not mention 'hierarchical modeling' as another option in Bayesian framework. Hierarchical modeling is another option that allows augmentation of external information under some reasonable assumptions of exchangeability.	Some discussion or at least acknowledgment of hierarchical modeling as another option in Bayesian framework would provide more complete picture of Bayesian frameworks relevant for borrowing external information.
Section 4.3.7 Lines 871-874	We agree that there is a need to justify why external data can be incorporated into the analysis. Formally analyzing data together either via Bayesian methods and informative priors, or via frequentist meta-analysis would only be appropriate if the similarity of response to intervention between reference and target populations has been demonstrate. The guidance should discuss how to assess this similarity.	
V. ADDITIONAL PEDIATRIC EXTRAPOLATION PLAN CONSIDERATIONS		
Lines 927-937	It is unclear what safety endpoints should be considered for extrapolation. Treatment Emergent Adviser Events (TEAE) is a common safety endpoint but could contain different AEs for target and source populations.	We suggest including additional considerations on safety endpoints used for extrapolation through training materials.
Lines 958-963	"If the disease and response to treatment are sufficiently similar, the adolescent and adult populations can be combined into a single analysis of efficacy. The purpose and statistical methods for a separate analysis of the adolescent subgroup should be carefully considered so that any identified differences or uncertainties are addressed. Such subgroup analyses should be interpreted cautiously; the strength of any conclusion about the extrapolation of efficacy (or lack thereof) based solely on exploratory	We suggest including additional considerations regarding adolescent sample size especially when included in adults studies as well as inclusion of adolescents in long term safety follow-up.

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	subgroup analyses may be limited (see ICH E9)."	
Lines 986-989, Section 5.2	The inclusion of adolescents might help with the initiation (dose selection) of a pediatric study that targets 10+ year-old participants; not for every age cohort. For younger age cohorts, an IA (rather than extrapolation) might be necessary to optimize the dose for these participants.	Consider changing the word "should" in line 989 to "may".
Lines 996-997, Section 5.2	It would be good to emphasize in paranthesis (30-40kg, 40-50 kg etc.). Because, in several cases, EMA seems to be specifically focused on 30-40 kg body weight groups.	Consider rephrasing to "In such situations, specific consideration pertaining to the impact of lower body weight (eg. 30-40 kg, 40-50 kg etc.) in adolescents should be carefully considered."
Lines 1014-1017, Section 5.2	Inclusion of adolescents into an adult trial could significantly delay the completion of the adult trial (especially if stratified by age or require a certain number of adolescents) and thus delay the time of getting the drug to the general patient population (often a larger population than adolescents) to receive the benefit of the drug. A separate adolescent trial may not have enough patients due to rarity of disease in this age group and thus lack sufficient sample size to demonstrate the efficacy/safety. In addition, the sponsor often has challenge to gain permission from local health authorities and/or local ethical committees for conducting adolescent study without confirmatory efficacy in adults. Please consider whether it is necessary to have “strong justification” for every adult study on why adolescents are not included or studied in parallel.	We suggest revising the last sentence. For example, “when the disease and response to treatment are sufficiently similar between adolescent and adult subjects, adolescents being included in an adult clinical trial or studied in a parallel trial is strongly encouraged". Also, consider adding a clause in to the effect of, “When the inclusion of adolescent patients into an adult trial would not slow down the development of the agent for [any target population/reference population], the inclusion of adolescents into adult trials should be strongly considered. This is particularly important when incidence of a given disease is extremely rare in the adolescent population, making an independent adolescent or pediatric study unfeasible. Alternatively, an adolescent trial could be run in parallel…"