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0	0		It could be useful to add some references or indications/recommendations for performing extrapolations between two pediatric age-related sub-populations (i.e., pre-school vs school pediatric patients)	
0	0		it may be much clearer to use 'pediatric population' to replace 'target population' and use 'adult population' to replace 'reference population' in the whole document. At least, we can save some space with the replacements.	
0	0		One of the objective of the guideline is to harmonize the approaches to pediatric extrapolations. The guideline explains that a comprehensive safety plan, including the need for pre- and post-marketing safety data collection should be described in the extrapolation plan. However, the guideline do not provide details for the type of post marketing safety studies to be conducted.	It would be helpul to discuss the different types of post marketing to be studied, and to provide examples. The conduct of postmarketing studies (e.g. registries) has limitations and might be very challenging to be put in place, especially when the treated population is expected to be low, or when no specific safety concern has been identified based on data in adults. Further guidance would be helpful, especially for patients under 2 years of age.
0	0		It is not clear to me whether the Extrapolation Plan is an internal document that supports pediatric developmnet strategey or if it must be submitted as component of PIP or PSP. In this case, should Extrapolation Plan updates be part of PIP or PSP amendments.	
0	0		General comment: adding a reference to the guideline where the paediatric population is defined would be welcomed	
0	0		The focus of this guidance is on the extrapolation of adult treatment effect to pediatric population. Nonetheless, there may be different approaches for pediatric medication development. For some disease areas (particularly for a pediatric disease), a well control clinical trial may be directly used to demonstrate the treatment effect for pediatric population and there is no need for the extrapolation. Please discuss.	
0	0		General comment: We only have a few minor comments. In general, it is comprehensive and more practical from sponsor's aspect, comparing with previous guidance.	
4	9	1.1	A multi-regional trial strategy is often applied for global new drug development for adult population. Treatment effects of some of the regions can be extrapolated to a specific region for the regional approval. For global access to a pediatric medicine, a similar approach may be used for a pediatric program. Certain discussion on how to extrapolate the treatment effects of some of the regions to a specific region for adult population and then extrapolate the effect to the pediatric population of the region may be helpful.	
13	17	1.2	As per definition, disease similarity is a condition for extrapolation. However, there should be no pre-established condition for extrapolation. As knowlegde evolves we may more an more face situations where a profound understanding of the differences may still allow for extrapolation. Another situation to be consider relates to the development of insulins for children with T2DM. Clinical trials in this population are not required. Intead we conciously or subsconciouly extrapolate efficacy and safety from the clinical data in children with T1DM and available evidence/data of treatment with other insulins in adults and children with T2DM.	"an approach for optimizing the generation of evidence in support of effective and safe use of drugs in the pediatric population."
22	22	1.2	Can ICH provide a few examples regarding safety extrapolation?	
50	50	1.3	add reference sections here	
82	83	1.4	The meaning of "adequate and well-controlled trial(s)" in this figure is unclear. What does "well-controlled" mean? As a single-arm study is included in the efficacy studies for pediatrics in Section 4.3, it does not mean controlled studies are always required. Does it mean the most strict case for studies in peciatrics?	The wording and/or this figure needs to be clarified. Or, Section 4 should be referred.
97	97	2	The meaning of "strength of the known data" is unclear. Some more clarification should be needed for this wording.	Need some more clarification for this wordking to help understanding.
102	102	2	it is confusing here. "extrapolation" and "data generations" are two different concepts. should use a different term rather than "extrapolation plan".	
122	216	3.1	Since disease similarity is independent of the drug being developed, please include a list of pediatric diseases which are considered as adequately similar to adult diseases based on current evidence to support extrapolation. 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).	
160	160	3.1.1	insert "age-related ontogeny"	
189	189	3.1.1	In the subsection *Course of the disease* . I propose to add an item: Are the spontaneous evolution/progression of the disease, when it is not treated, the same in both the reference and the target populations?	
217	217	3.2	propose to change "drug pharmacology similarity" to "PK/PD Similarity"	

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241	243	3.3	proposed changes in the text in red	Similarly, data generated in other indications for the drug, in pediatric use, can serve as a relevant source of knowledge, principally for the safety, when assessing the similarity or difference of response to treatment.
243	245	3.3	For safety concern, a reduced dose may be used for pediatric population. Then the treatment effect of a higher dose for the adult population may not be directly extrapolatable to the pediatric population particularly if there is clear E-R relationship for the adult population. Then a PK-response modeling approach may be used for the extrapolation.	
253	262	3.3.1	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. 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.	
351	351	3.5.1	The meaning of "as part of this analysis" is unclear. Does it mean "as part of extrapolation of safety data to the target population"?	Need some more clarification for this wordking to help understanding.
357	364	3.5.1	Regarding the safety knowledge of the product, I think that some reference to how long the product has been on the market could be done. In fact, the safety of old products is normally well known.	
361	361	3.5.1	The age range for "adelescents" should be clarified as it can differ depending on the country/region.	The age range for adolescents in this guideline should be clarified.
366	393	3.5.1	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.	
375	375	3.5.1	insert "are the known safety effects mechanism related?"	
380		3.5.1	proposed changes in the text	How does the expected treatment duration/dose and treatment effect size in the reference
399	399	3.5.1	can examples be added here? we are always asked to collect safety data in pediatric trials.	
407	407	3.5.2	for very young pediatric population, due to ontogeny changes, the safety profile may change. need to add a statement in.	
420	420	3.5.2	insert: for some indications, due to recruitment challenges, the sample size may be limited without considering statistical power.	
430		3.6	proposed changes in the text in red	Integration of existing evidence involves a comprehensive review to evaluate the similarities/differences
498		3.7	proposed changes in the text in red	similarities and differences between the reference and target populations, the current knowledge gaps
514	515	4	proposed changes in the text in red	Once a pediatric extrapolation concept has been developed, the relevant proposed (or needed or necessary) study(ies) should be detailed in the extrapolation plan. The rational of each study -the reason for been proposed- should be clearly described. The design of the study(ies) should reflect the information…

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522		4.1	proposed changes in the text in red	Evaluation and selection of an appropriate dose for each pediatric age subgroup (when applicable), to be studied is critical to achieve target
545	557	4.1	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 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 dose adjustments to be implemented early in the study if PK is found to be different than expected.	
548	548	4.1	The wording of "separate PK studies (or study)" needs to be clarified in this document. Does it mean clinical trials whose main objectives include PK or clinical trials with dense PK samplings?	It seems that separate PK studies mean clinical trials whose main objectives include PK analysis. But, it may be used as opposite to sparse PK sampling design from the next sentence.
549	549	4.1	"Some age range" needs to be clarified.	It is unclear from this document, and needs to be specified.
550	553	4.1	Instead of a separate PK study, efficacy/safety studies with dense PK sampling design can be alternatively considered.	Extensive PK data can be obtained also from efficacy/safety studies.
583	585	4.1.2	it is often the case where a biomarker or secondary endpoint is used for the trials of both populations. But the data for the clinical endpoint is very limited for pediatric program given the much smaller sample size.	
597	600	4.1.3	EMA is more precise here, saying :" The theoretical values of allometric exponents (0.75 for clearance and 1.0 for volume of distribution) are considered to have physiological basis [1], and often provide adequate explanation for body weight relationships in paediatric patients [2,3]. The exponents are often estimated and for different reasons these estimates may differ from the theoretical values. In neonates the maturation level of eliminating organs influences the estimates and in adults the body composition will affect them."	it would be helpful to have a statement regarding the acceptance of theoretical values in scaling approaches
640	640	4.1.3.1	insert: as well as samples size.	
648	650	4.1.3.1	Consider replace "means" by "median" and "differences" by "ratios" for the analysis and reporting of similarity.	*An evaluation of confidence intervals for the median ratios in key exposure metrics such as AUC and Cmax could be an acceptable approach.*
654	654	4.1.3.1	add: due to small sample size	
655	657	4.1.3.1	"In addition, inter-individual variability needs to be considered in establishing exposure similarity rather than comparing means alone" : does this mean that similarity in outer percentiles must be considered also ?	
687		4.1.3.2	proposed changes in the text in red	have ~~confidence~~ confirmation that there is a relationship between the biomarker effect and efficacy in the
733	737	4.2	What kind of plan is anticipated here? Is this also at the stage of PIP/iPSP to show what is planned in terms of simulations with models constructed at the stage of EOP2?	A clarification as to what content is expected at this stage would be good. At the regulatory decision stage some simulations were probably already performed. Is this when also a report would be needed?
739	744	4.2	"The availability of the various data sources dictates, in part, the methodologic approach…"	This sounds like there is a common rule as to what modelling approach should be used. However, both top-down and bottom-up approaches have their own caveats. With pediatric modelling often being started after adult data has been generated this reads very much in favor of top-down approaches. Is this the agencies intention?
746	752	4.2	"the specific characteristics of the target population, such as relevant body size and organ maturation, should be incorporated in the model."	To show how a model behaves across a virtual population, one option is using the NHANES database, which is US children and their body measures. Also this is an overall survey, so not disease specific, which can have an influence on expected body measure distribution in some indications. Is there a common recommendation as to what data sources should be used to create virtual populations? Recommended databases for example?

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751	752	4.2	Bayesian approach with the capability to make probabilistic statement is particular useful when the threshold for similarity cannot not be easily defined. It provides the probabilities of reaching different thresholds (Bayesian analysis is mentioned again around line 918. why not to consolidate the method in one place?)	
761	764	4.2		Could be more clear on what is expected in terms of assumption testing? Are these Simulations, Sensitivity analyses? Multidisciplinary input?
770		4.2	“Collecting additional data”	Is this adult data? We try to limit pediatric data as much as possible, so this means going back into the adult population and collect relevant data to reduce parameter uncertainty?
789		4.3.1	proposed changes in the text in red	The sample size of studies should be calculated as the minimal number of subjects to ensure the threshold is met, or to ensure that
789	790	4.3.1	not matter how large the sample size is, we cannot ensure 100% probability to meet the threshold due to variability.	
827	831	4.3.3	one approach for similarity assessment is to check whether the point estimate of treatment effect for the pediatric population is least certain proportion of the effect for the adult population (ICH E17). There is no formal hypothesis and the associated type I error rate.	
935	935	4.3.7	tipping point analysis usually change the point estimate rather than the variability or effective sample size in the analysis	
970		5.1	proposed changes in the text in red	of safety for each pediatric age subgroup and a thorough justification to support any conclusions about the acceptability to
980		5.2	proposed changes in the text in red	The enrollment of adolescents (11-14 years) into adult clinical trials may hasten adolescent access to safe
991	992	5.2	In this line, I have the impression that pediatric population is considering any patient less than 18 years. Since my point of view, this definition has to be clarified.	

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995		5.2	"Additional data to inform adolescent dosing may not be necessary as the adolescent and adult PK are generally similar. In such situations, specific consideration pertaining to the impact of lower body weight in adolescents should be carefully considered	There is no comment on the dose selection for these adolescents here. The FDA states for inclusion of adolescents into adult oncology trials: The following are recommendations for dosing based on how the drug is dosed in adults: • For drugs with body size-adjusted dosing for adults, adolescent patients should receive the same body size-adjusted dose (mg/kg or mg/m2) that is administered in adults. • For drugs administered as a fixed dose based on data showing no clinically meaningful body size effect on drug exposure and toxicity in adults, a minimum body weight threshold should be defined to prevent adolescent patients who have a lower body weight than average from exceeding adult exposures. An FDA analysis of adult population pharmacokinetics of oncology drugs suggested that 40 kg (the approximate median body weight of a 12-year-old4) is generally the lower end of the body weight range that has no clinically relevant effect on drug pharmacokinetics or safety. (This cutoff may change based on the characteristics of the drug, including the effect of body size on pharmacokinetics, the therapeutic index, and dose- and exposure-response relationships.) In general, adolescent patients who weigh at least 40 kg can receive the same fixed dose administered in adults. Do we need to perform simulation studies every time we include adolescents? Could there be a general rule included here?
1014	1017	5.2	if the responses to treatment are sufficiently similar between the adolecent and adult populations, there should be no need for a parallel trial for adolecents.	