

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH HARMONISED GUIDELINE**

**PEDIATRIC EXTRAPOLATION**

**E11A**

Draft version

Endorsed on 4 April 2022

*Currently under public consultation*

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.*

**E11A**  
**Document History**

<b>Code</b>	<b>History</b>	<b>Date</b>
E11A	Endorsement by the Members of the ICH Assembly under <i>Step 2</i> and release for public consultation.	4 April 2022

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**ICH HARMONISED GUIDELINE**  
**PEDIATRIC EXTRAPOLATION**

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**ICH Consensus Guideline**

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1 **1. Introduction**

2

3 **1.1 Objectives of the Guideline**

4 The purpose of this guideline is to provide recommendations for, and promote international  
5 harmonization of, the use of pediatric extrapolation to support the development and  
6 authorization of pediatric medicines. Harmonization of the approaches to pediatric  
7 extrapolation should reduce the likelihood of substantial differences between regions.  
8 Importantly, harmonization should also reduce exposure of pediatric populations to  
9 unnecessary clinical trials and facilitate more timely access to pediatric medicines globally.

10

11 **1.2 Background**

12 Regional guidelines discussing pediatric extrapolation have previously been issued by various  
13 regulatory agencies. Pediatric extrapolation is defined in the ICH E11(R1) guideline as “an  
14 approach to providing evidence in support of effective and safe use of drugs in the pediatric  
15 population when it can be assumed that the course of the disease<sup>1</sup> and the expected response to  
16 a medicinal product would be sufficiently similar in the pediatric [target] and reference (adult  
17 or other pediatric) population.” Pediatric extrapolation can extend what is known about the  
18 reference population (e.g., efficacy, safety, and/or dosing) to the target population based on an  
19 assessment of the relevant similarities of disease and response to therapy of the two  
20 populations.

21

22 Historically, extrapolation of safety generally was considered unacceptable. However, our  
23 understanding of similarities and differences between reference and target populations with

---

<sup>1</sup> For the purposes of this document “disease” includes both “diseases” and “conditions”

24 respect to safety has evolved. As described in the ICH E11(R1) guideline, the principle of using  
25 data generated in a reference population to define the scope and extent of data that should be  
26 collected in a target population can also apply to the generation of safety data (see section 3.5).

27

28 This guideline is intended to complement and expand on ICH E11(R1) to provide a more  
29 comprehensive framework for the use of pediatric extrapolation in optimizing pediatric drug  
30 development. This guideline provides a roadmap to aid drug developers and regulators on the  
31 degree to which pediatric extrapolation can be applied, and the information that should be  
32 collected to address gaps in knowledge supporting the safe and effective use of medicines in  
33 the pediatric population.

34

### 35 **1.3 Scope**

36 This guideline provides a framework for using extrapolation as a tool to support pediatric drug  
37 development that encompasses an iterative process for understanding the existing information  
38 available, the gaps in information needed to inform development and ways to generate  
39 additional information when needed to support extrapolation for pediatric drug development.  
40 This guideline recommends approaches to assessing factors that influence the determination of  
41 the similarity of disease and response to treatment between a reference and pediatric target  
42 population. In addition, it discusses how the characteristics of the disease, drug pharmacology  
43 and the response to treatment may influence this determination.

44

45 The guideline discusses how the use of statistical and other quantitative tools (e.g., modeling  
46 and simulation) may be leveraged to fill in gaps in knowledge. This guideline is not intended  
47 to provide a comprehensive listing of all the situations where extrapolation of data can play an  
48 important role in pediatric drug development, but it does explain how pediatric extrapolation  
49 can be applied practically to support the safety and efficacy of a product in pediatric  
50 populations. This guideline does not discuss other types of “extrapolation” – for example, the

51 ICH E5 guideline should be consulted regarding the concept of "bridging studies" to leverage  
52 foreign clinical data from one region for extrapolation to another region's population as a basis  
53 for registration of a medicine. Although there are some quantitative strategies mentioned or  
54 explained within the guideline, it is not meant to be a comprehensive instruction guide. Some  
55 basic understanding of the role of quantitative approaches used in clinical trial development is  
56 expected.

57

#### 58 **1.4 General concepts**

59 The use of pediatric extrapolation ensures that children only participate in clinical trials when  
60 necessary to further the scientific understanding of a medicinal product's use in children. As  
61 per ICH E11(R1), a sufficient prospect of clinical benefit is required to justify the risks of  
62 exposing children to an investigational product. When regulatory authorities require pediatric  
63 studies as part of adult-driven drug development, the rationale for doing so can implicitly  
64 assume a degree of similarity between the reference and target (in this case pediatric) condition.  
65 Thus, it may be appropriate for a pediatric program for diseases associated with an adult  
66 condition to incorporate some degree of pediatric extrapolation.

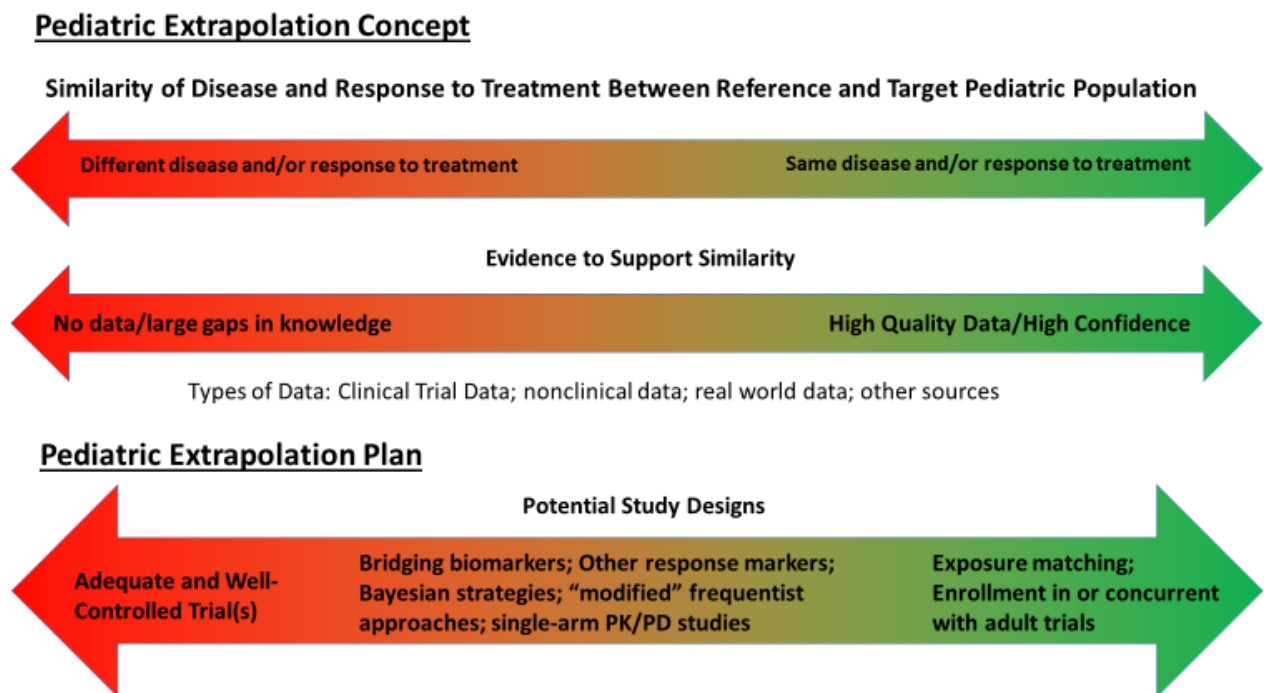
67

68 In the ICH E11(R1) definition of pediatric extrapolation, "sufficiently similar" might suggest  
69 a threshold that must be exceeded for pediatric extrapolation to be acceptable for regulatory  
70 consideration. However, whether the course of disease and expected response to treatment can  
71 be considered sufficiently similar between a target and reference population is not simply a  
72 "yes or no" question. Therefore, this guidance does not use discrete categories (e.g., full, partial  
73 or none) to describe the different approaches to pediatric extrapolation, in favour of identifying  
74 the clinical trial designs which can address the remaining uncertainties based on an assessment  
75 of the existing data. The use of extrapolation as discussed in this guideline reflects that a  
76 continuum of dissimilarity/similarity may exist. There may be uncertainties associated with the  
77 data supporting extrapolation to the target pediatric population. The extrapolation approach  
78 should address these uncertainties, utilizing clinical judgement to establish the tolerable level

79 of uncertainty that will be acceptable (see Figure 1). Options for trial designs will depend on  
80 the level of uncertainty that needs to be resolved.

81

82 **Figure 1: Pediatric Extrapolation Approach**



83

84

## 85 2. Pediatric Extrapolation Framework

86 The extrapolation framework consists of three parts: development of a pediatric extrapolation  
87 concept; and the creation and execution of a pediatric extrapolation plan (see Figure 2).

88

89 The first step is the development of a pediatric extrapolation concept. The concept is developed  
90 through comprehensive and detailed review of existing information about the range of factors  
91 that define the disease, the drug pharmacology, and the clinical response to treatment across



92 the reference and target populations. Factors that influence the effects of treatment in the  
93 reference and target populations should be identified. Once a review of the existing knowledge  
94 has been conducted, the data should be synthesized to develop the pediatric extrapolation  
95 concept. Methods to review and synthesize these data can include quantitative approaches such  
96 as statistical methods and modeling and simulation. Synthesis of the data should be conducted  
97 to both understand the strength of the known data as well as to identify important gaps in  
98 knowledge which will inform what additional data, if any, are required.

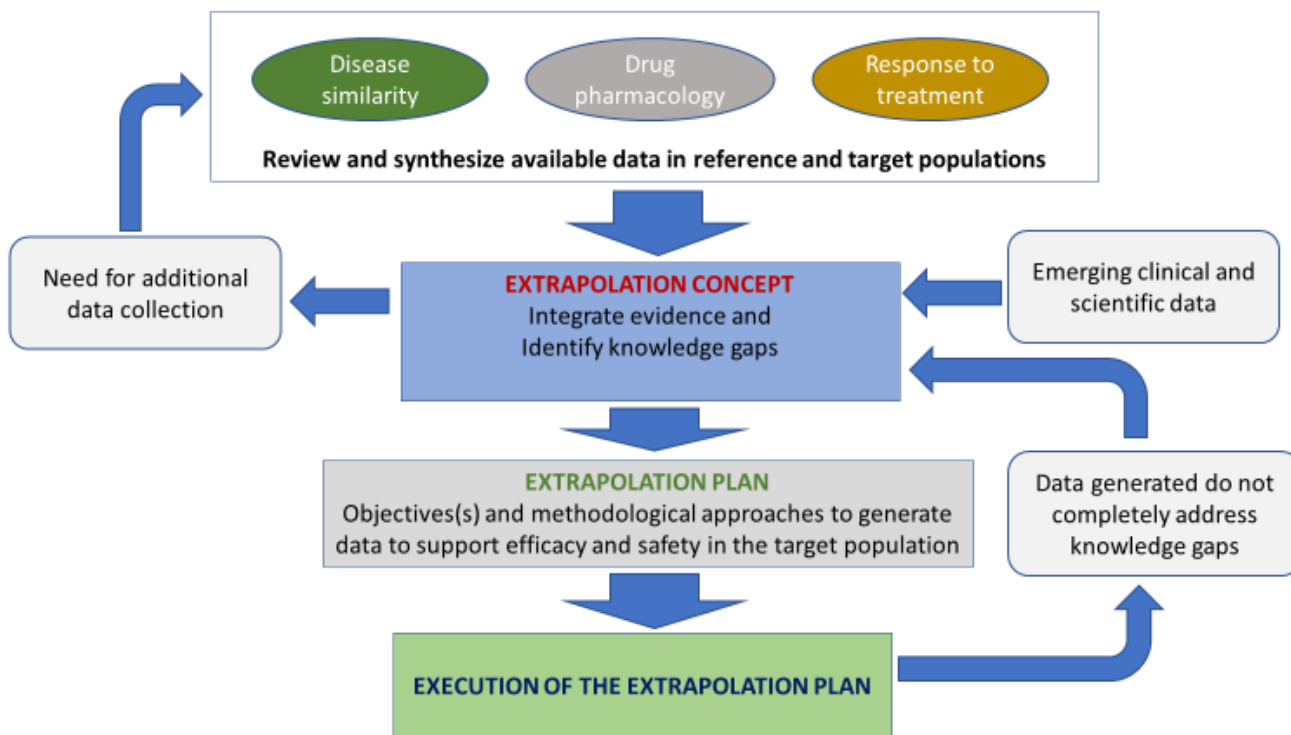
99

100 Once the pediatric extrapolation concept has been developed, the pediatric extrapolation plan  
101 should be developed. This plan should include the objectives(s) and methodological  
102 approaches for the data that need to be generated to support efficacy and safety in the target  
103 population for the purpose of regulatory decision-making. In addition, there may be an  
104 evolution of the pediatric extrapolation concept based on emerging clinical and scientific data.  
105 Rather than abandon an existing pediatric extrapolation plan based on a prior concept, the plan  
106 itself can be modified to reflect current scientific and clinical understanding.

107

108

109 **Figure 2: Pediatric Extrapolation Framework**



110

111

112 The execution of the plan should also include a review of the data generated to confirm any  
113 assumptions made and to address uncertainties identified in the pediatric extrapolation concept.  
114 A review of the results should also be used to identify whether a different approach can be  
115 considered in pediatric extrapolation plans for subsequent pediatric development programs.

116

### 117 **3. Pediatric Extrapolation Concept**

118 Development of a pediatric extrapolation concept requires an understanding of the factors that  
119 influence the similarity of disease, the pharmacology of the drug and the response to therapy  
120 as well as the safety of use in all the relevant populations.

121

122 **3.1 Disease Similarity**

123 The assessment of similarities and differences of the disease between a reference and target  
124 population is a key factor in developing the pediatric extrapolation concept. Although  
125 historically, pediatric extrapolation was often based on a binary determination of disease  
126 similarity (i.e., either yes or no), the understanding of similarities and differences in disease  
127 between a reference and target population has become more nuanced (see Figure 1, Section  
128 1.4).

129

130 The evaluation of disease similarity is not intended to determine whether the disease in the  
131 reference and target populations is “exactly the same” but rather whether the disease is different  
132 to a degree that would preclude pediatric extrapolation. Even if there are differences in the  
133 disease, some similarities may be present that would still allow for the use of pediatric  
134 extrapolation.

135

136 It can also be possible to identify disease subgroups in both the reference and target populations  
137 that are sufficiently similar to support the use of pediatric extrapolation even if the disease in  
138 the overall population is not sufficiently similar. For example, anatomic congestive heart  
139 failure in children is not similar to adult heart failure, whereas heart failure due to dilated  
140 cardiomyopathy is similar between adult and pediatric populations, allowing for extrapolation  
141 from adult to pediatric patients with dilated cardiomyopathy.

142

143 To increase confidence in understanding the similarity of disease between the populations,  
144 evaluation of disease similarity should also attempt to determine the gaps in knowledge and  
145 uncertainties that exist in the evidence reviewed and identify what additional evidence is  
146 needed. Importantly, the evaluation of disease similarity is not a static or “one-time” exercise.  
147 As knowledge is gained, the additional knowledge should be incorporated into the evaluation  
148 of disease similarity in the pediatric extrapolation concept.

149

150 **3.1.1 Factors to Consider in the Evaluation of Similarity of Disease**

151 Assessment of disease similarity between a pediatric population and a reference population  
152 should include a review of the following factors:

153

154 ***Pathophysiology of disease***

155 Evaluation of the pathophysiology and etiology of the disease between the reference and target  
156 populations should be conducted. Collection of relevant information may include biochemical,  
157 genetic/epigenetic, cellular, tissue, organ system, and epidemiologic information that describes  
158 similarities and differences between the reference and target populations. Evaluation can also  
159 include a determination about whether differences in the clinical presentation of disease may  
160 depend upon the age of onset, age-dependent phenotypic expression, or other age-related  
161 differences. Evaluation of biomarkers that are common in the pathophysiology of the disease,  
162 including disease progression, if available, are often helpful in establishing similarities in a  
163 disease between the reference and target pediatric populations. Similarities in the outcome of  
164 untreated disease should also be evaluated.

165

166 ***Disease definition***

167 Evaluation of disease definitions and diagnostic criteria between the reference and target  
168 populations should be conducted. When evaluating similarities and differences between  
169 reference and target populations, the following should be considered:

- 170
- What are the manifestations or diagnostic criteria that define the disease?
- 171
- How similar are the manifestations between the reference and target pediatric  
172 populations?  
173

174

- 175       • How are the manifestations measured?  
176  
177       • Are there similar measurements used to define manifestations of the disease in the  
178       reference and target pediatric populations?  
179  
180       • Are there subtypes (e.g., based on severity, genetics, molecular markers, etc.) of the  
181       disease that occur in the reference or target populations?  
182  
183       • What are the similarities and differences in the subtypes of the disease in the reference  
184       and target population?  
185  
186       • Are there other factors to consider (e.g., genetic/epigenetic, etc.) that are needed to  
187       define the disease?  
188

189    *Course of disease*

190    Evaluation of the similarities and differences in the course of disease between reference and  
191    target populations should be conducted. In the evaluation, the following should be considered:  
192

- 193       • What are the similarities and differences of the clinical course of the disease between  
194       the reference and target populations? Are there differences in the course of the disease  
195       based on factors such as the age of onset of the disease?  
196  
197       • Are there similar endpoints and/or biomarkers available that help to measure  
198       progression of disease in both the reference and target populations?  
199  
200       • Are the short-term or long-term outcomes of the disease similar for the reference and  
201       target pediatric populations and can these outcomes be measured similarly?  
202  
203       • Are there available treatments being used for both reference and target populations?  
204

- 205       • What effect have these treatments (e.g., timing of treatment relative to onset of disease  
206           and age of the patient, frequency of treatment, length of treatment) had on the course  
207           of the disease in the reference and target populations?  
208

209   Although the frequency, severity, or timing of the progression of the disease may differ  
210   between the reference and target populations, certain commonalities in the course of the disease  
211   may still allow for the use of pediatric extrapolation. For example, if a treatment becomes  
212   available that changes the course of the disease in the reference population, but the treatment  
213   has not yet been approved in the target population, this should not lead to the conclusion that  
214   the course of the disease between the two populations is now different for the purposes of  
215   pediatric extrapolation.

216

### 217   **3.2 Drug (Pharmacology) Similarity**

218   As part of an evaluation of the similarities and differences of the pharmacology of the drug  
219   between the reference and target populations, it will be critical to review what is known about  
220   the underlying absorption, distribution, metabolism, and excretion (ADME) properties and  
221   mechanism of action (MOA) of the study drug. Consideration should be given to the potential  
222   influence of body size (e.g., weight, body surface area [BSA]), age, organ maturation,  
223   concomitant medications, and other relevant covariates on ADME (e.g., protein binding,  
224   metabolic enzymes, transporters, renal function) and MOA properties (e.g., expression level  
225   and sensitivity of drug targets).

226   Differences in ADME processes can result in differences in pharmacokinetic (PK) parameters  
227   and resulting drug exposure. Exposure is a broad concept, ranging from measurement of the  
228   systemic (or other biological compartment) exposure of the drug (parent and/or metabolite(s)),  
229   at a single point in time (for example maximum or trough concentration), exposure over a time  
230   interval (for example  $AUC_{0-t}$  or average concentration), or characteristics of the overall  
231   concentration-time curve (e.g., clearance, volume of distribution). In addition, differences in  
232   MOA properties can result in differences in an exposure-response (E-R) relationship between

233 the reference and target population. Changes in these characteristics over time due to  
234 developmental maturation should be considered.

235

### 236 **3.3 Similarity of Response to Treatment**

237 As with similarity of disease, the similarities, and differences in response to treatment between  
238 a reference and target population should be understood as a continuum (see Figure 1, Section  
239 1.4). To assess similarities and differences of response to treatment, a thorough review of  
240 available knowledge in both the reference and target populations should be conducted,  
241 including the response to the drug, other drugs in the same class and in other classes. Similarly,  
242 data generated in other indications for the drug can serve as a relevant source of knowledge  
243 when assessing the similarity or difference of response to treatment. An evaluation of data that  
244 inform exposure-response (E-R) relationships between the target pediatric population and the  
245 reference population should be part of this assessment.

246

#### 247 ***3.3.1 Factors to Consider in the Evaluation of Similarity of Response to Treatment***

248 The degree of similarity of response to treatment between the reference and target populations  
249 can also influence the degree of similarity of disease and vice versa. Assessment of similarity  
250 of response to treatment between a target pediatric population and a reference population  
251 should include a review of the following factors:

252

##### 253 *Pharmacokinetics and pharmacodynamics (PK/PD)*

254 The potential effect of developmental and maturational changes on the PK/PD relationship and  
255 clinical response should be evaluated. An understanding of the drug target and its role in  
256 normal development, disease pathology and expected response to therapy should be evaluated.  
257 For example, if a receptor does not exist in the first 6 months of life, no response to treatment  
258 would be expected for a drug only targeting this receptor in this age group. Factors that impact

259 response that may differ between the reference and target populations (e.g., concomitant  
260 medications, comorbid disease, organ function, genetic makeup) should be evaluated to assess  
261 whether there is an impact on the extent to which pediatric extrapolation can be applied.

262

263 *Response endpoint(s):*

264 When evaluating the similarity of response, the following questions should be considered:

265

266 • How is a response endpoint (e.g., clinical, biomarker, composite, etc.) measured in the  
267 reference and target populations?

268

269 • Is there a similar measurement of the endpoint used in both the reference and target  
270 populations?

271

272 • If the response endpoint or measurement of the endpoint is different in the reference  
273 and target populations, what is the relationship between the endpoints (e.g., clinical  
274 endpoint in the reference population in relation to a biomarker endpoint in the target  
275 population)?

276

277 When attempting to evaluate similarity of response to treatment, it may be that consideration  
278 should be given as to whether there may be age/maturity-related factors that could result in  
279 differences in the measured response between the target and reference populations. For many  
280 pediatric drug development programs, the primary endpoint(s) in the target pediatric population  
281 is/are different from that in the reference population. When this is the case, a comparison of  
282 one or more components of the primary endpoint(s) and/or secondary/exploratory endpoint(s)  
283 can be used to understand the relationship between the different endpoints.

284



285 **3.4 Sources and Types of Existing Data**

286 Use of existing data should be fit-for-purpose (i.e., the context in which it was generated is  
 287 applicable to the context in which it is intended to be used). It is important to consider both the  
 288 quantity and quality of data to evaluate the similarities and differences between the reference  
 289 and target populations. All available data should be used to establish the extrapolation concept  
 290 and formulate the extrapolation plan. Such information may also include data from ongoing  
 291 adult/pediatric development programs, or relevant data from terminated programs. Examples  
 292 of the sources and types of data that should be evaluated are included in Table 1 and are  
 293 discussed further in this section. Given the considerable overlap in the data used to support  
 294 similarities and differences in disease, pharmacology, and response to treatment, the sources  
 295 of data are combined in Table 1.

296

297 **Table 1: Examples of Sources and Types of Data to Evaluate for Similarity of Disease**  
 298 **and Response to Treatment**

Sources of Data	Types of Data
<b>Clinical data</b>	PK, PK/PD, E-R, and clinical data in the same condition for a drug or drugs in the same class
	PK, PK/PD, E-R, and clinical data in other related conditions for a drug or drugs in the same class
	PK, PK/PD, E-R, and clinical data in the same condition for a drug or drugs in a different class
<b>Nonclinical data</b>	ADME Data from animal models
	<i>In silico</i> , <i>in vitro</i> , and <i>in vivo</i> data (e.g., disease-response, PK, PK/PD, semi-mechanistic, and mechanistic)
	Juvenile nonclinical toxicology data
<b>Real World Data</b>	Data including but not limited to disease registries (regional, national, and international), electronic health records, health claims databases

<b>Other sources</b>	Systematic reviews or meta-analyses including those that can be used to evaluate suitable biomarkers
	Professional organization guidelines/Clinical practice guidelines/Consensus documents
	Published models/simulations (e.g., PK/PD, mechanistic)
	Expert opinion
	Standard of care/practice of medicine

299

300 *Clinical data*

301 Clinical data (e.g., from controlled trials, prospective observational studies, PK, PK/PD and/or  
302 biomarker studies) in populations with the same condition or related conditions should be  
303 evaluated to understand similarities and differences between the reference and target  
304 populations. All available data for the drug/drug class should be evaluated including ongoing  
305 and completed studies, published or unpublished, whether results are positive or negative.

306

307 *Nonclinical data*

308 Data from nonclinical sources such as *in vivo*, *in vitro*, and *in silico* models should also be  
309 evaluated when available. Data from *in silico* models may also include PK and/or PD, semi-  
310 mechanistic, and mechanistic models. In general, when clinical data are available, data from  
311 animal models may be less relevant, but this is not always the case. In certain situations, disease  
312 similarity can be supported with only nonclinical data, especially when there is no ability to  
313 collect clinical data (e.g., anthrax or plague).

314

315 *Real world data (RWD)*

316 The extent to which RWD can be used to support pediatric extrapolation, both the pediatric  
317 extrapolation concept and plan, is evolving. Therefore, the adequacy, relevance, and extent to

318 which RWD can be used to support pediatric extrapolation should be discussed with regulatory  
319 authorities. In the development of the pediatric extrapolation concept, a review of data from  
320 RWD sources including but not limited to electronic health records, claims databases, and  
321 registries, can be considered. The use of RWD in an extrapolation plan is discussed later (see  
322 section 4.3.2)

323

324 *Other sources*

325 Expert opinions, including clinical practice guidelines developed by professional  
326 organizations, can be used to support the extrapolation concept. Published clinical practice  
327 guidelines from professional organizations are considered more informative than unpublished  
328 expert opinions. However, published guidelines and expert opinions can vary between regions  
329 based on differences in standard of care. Reliance on expert opinion or standard of care without  
330 an assessment of the strength of the evidence is generally not sufficient.

331

332 The sources and types of data that are described above each have strengths and weaknesses.  
333 The confidence in the degree to which the sources and types of data support similarities  
334 between the reference and target populations require an assessment of the quantity and quality  
335 of data from each source as well as the context in which the data are being evaluated. A critical  
336 and multidisciplinary assessment of all the data should be conducted to justify the use of the  
337 evidence to support the extrapolation concept.

338

### 339 **3.5 Safety Considerations in the Extrapolation Concept**

340 Basic considerations for the development of an overall safety data collection and adverse event  
341 reporting plan are discussed in other guidance (ICH E2, ICH E6, ICH E11, ICH E11(R1)).  
342 This section describes specific considerations related to the extrapolation of safety as part of  
343 the overall development of the safety evaluation for a pediatric population(s).

344

### 345 *3.5.1 Extrapolation of Safety*

346 The principles underlying the appropriate use of data generated in a reference population(s) to  
347 define the scope and extent of efficacy data that needs to be collected in a target population can  
348 also apply to the generation of safety data (see section 1.2). Extrapolation of safety data could  
349 be considered based on the available knowledge of the known and/or potential safety issues in  
350 the reference population that are relevant to the target pediatric population. Other information  
351 (e.g., nonclinical, mechanistic) should be considered as part of this analysis. These data should  
352 help increase certainty about the expected safety profile of a drug in a particular pediatric  
353 population and determine if additional gaps in knowledge need to be addressed in the pediatric  
354 program. Evaluation of the suitability and extent to which safety will be extrapolated should  
355 be included in the extrapolation concept and plan.

356

357 The source and amount of safety data to support the extrapolation of safety data to a target  
358 population should be considered early in drug development planning. The reference  
359 population(s) can include children and/or adults exposed to the same drug or class of drugs.  
360 Data can also be leveraged in reference populations who have been treated with different dosing  
361 regimens and/or for different diseases/indications. Enrollment of adolescents in/or concurrent  
362 with the adult trials may allow for earlier evaluation of safety for the adolescent population  
363 (see section 5.2). The collection of safety data in adolescents may also provide important  
364 information to support the safe use of a drug in younger patients.

365

366 When considering extrapolation of safety, the following questions should be considered:

367

368 • What is the age-range of pediatric patients to be studied as part of the safety  
369 extrapolation?

370

371 • What amount/quality of safety data are available from the reference population?

372

373 • Are there known on- or off-target effects of the investigational drug relevant to pediatric  
374 safety?

375

376 • Are data needed to account for age-specific short- and longer-term adverse effects in  
377 pediatric populations, which may not have been identified in studies in the reference  
378 population?

379

380 • How does the expected treatment duration and treatment effect size in the reference  
381 population compare with the target pediatric population?

382

383 • How do the expected drug exposures in the reference and target pediatric populations  
384 compare? Does the exposure needed to target a specific PD effect or clinical  
385 response predict a specific toxicity in the target pediatric population?

386

387 • What information is already known from non-clinical (including mechanistic, in vitro,  
388 in-vivo) sources that can be leveraged to the target population?

389

390 • Are there other differences between the reference and target population that could limit  
391 the extrapolation of safety (e.g., a background therapy used in a target population that  
392 may potentiate a safety signal but is not used in the reference population)?

393

394 The amount of safety data that can be extrapolated will depend on the answers to these  
395 questions. Under certain circumstances, no additional safety data will need to be collected  
396 beyond that which has already been collected as part of the efficacy extrapolation approach.  
397 If there is confidence that the available safety data collected are sufficient and address the  
398 relevant safety questions, there is no need to collect additional safety data in a pediatric pre-  
399 authorization program (reference E11(R1)).

400

401 **3.5.2 Additional Safety Considerations**

402 After an assessment of safety extrapolation has been made, there may be a need to collect  
403 additional safety data over and above what has already been collected. This could be the case  
404 when there are remaining gaps and/or age-specific safety concerns in the target population  
405 (e.g., the effect of corticosteroids on reduction in growth velocity in prepubertal children with  
406 open epiphyseal growth plates). Consequently, it may be that longer-term safety data should  
407 be collected in target pediatric populations post-approval.

408

409 Special consideration should be given to the collection of pediatric safety data in certain  
410 situations. Examples include:

- 411 • When the drug is a new molecular entity for a new class of drugs
- 412 • When there are known on-target age-related safety concerns
- 413 • When there are significant safety findings noted in the reference population that  
414 would be of special importance in children
- 415 • When the drug has a narrow therapeutic index

416

417 Ultimately, the design of the study(ies) that should be conducted will depend on the identified  
418 gaps in knowledge regarding the safety in the target population(s). Moreover, the use of  
419 arbitrary sample sizes without appropriate scientific justification is discouraged. Early  
420 discussion with regulators is recommended.

421

422 **3.6 Integration of Evidence and Development of the Pediatric Extrapolation Concept**

423 The goal of the development of the pediatric extrapolation concept is not only to determine the  
424 acceptability to use pediatric extrapolation but also to describe assumptions made, detail any  
425 gaps in knowledge, and assess the impact of uncertainties in the available evidence. This  
426 section provides guidance on the review, synthesis, and presentation of information that should  
427 be included in a Pediatric Extrapolation Concept.

428

429 *Integration of existing evidence*

430 Integration of existing evidence involves a comprehensive review to evaluate the similarities  
431 of the disease and response to treatment between a reference and target population. Once the  
432 evidence is reviewed and integrated, the strength of the evidence is evaluated and gaps in the  
433 evidence are identified. Integration of the evidence should address the following questions:

434

435 • What is the body of evidence and what is the clinical relevance of the evidence?

436

437 • What are the strengths and the limitations of the evidence?

438

439 • How consistent are the findings across the sources and types of data?

440

441 • What differences exist in the data and how do these differences affect assessment of  
442 similarity?

443

444 The answers to these questions will inform what additional information, if any, is  
445 recommended prior to finalizing an extrapolation concept and/or what additional data should  
446 be collected in the extrapolation plan.

447 *Methodologies that can be used to integrate evidence*

448 Quantitative synthesis of existing data should be used to integrate the evidence (see section  
449 4.2). Use of mechanistic and/or empirical approaches in the synthesis of data should be  
450 considered. Inclusion of systems biology/pharmacology data from the reference population(s)  
451 should be considered when population-level data (epidemiological, diagnosis and non-  
452 interventional study data) are available. Meta-analytic techniques for synthesizing efficacy data  
453 in the reference population(s) should also be considered.

454

455 There are a variety of approaches available for quantitatively evaluating the similarity of  
456 disease and/or response to therapy in different populations. The most appropriate method will

457 depend upon the parameters being evaluated for similarity assessment. Frequentist approaches  
458 to evaluate similarity of response between the reference and target populations can be informed  
459 by a comparison of point estimates and their associated confidence intervals. Given the  
460 different levels of precision typically available for estimating parameters in different  
461 populations, it will often be inappropriate to declare similarity purely based on overlapping  
462 confidence intervals. Communication of the manner in which uncertainty has been defined,  
463 specified, and otherwise accounted for in the model development and any simulations used to  
464 assess similarity of disease and/or response is recommended. In addition, any relevant  
465 assumptions with respect to the definition or expression of uncertainty should be specified.

466

467 Other exploratory analyses of the available data to assess similarity can also be considered. For  
468 example, if a trial conducted in a reference population has recruited across age groups,  
469 evaluation of the consistency of response in each age group can be considered. Approaches  
470 that can be used to evaluate the consistency of response across subgroups is described in other  
471 ICH guidance (ICH E17 section 2.2.7).

472

473 When evaluating similarity of disease and/or response between reference and target  
474 populations, the available data may not permit definitive conclusions to be drawn given the  
475 inherent uncertainties in the data. As such, it is recommended that sponsors discuss the  
476 acceptability of the proposed approach with regulatory authorities.

477

#### 478 *Knowledge gap identification*

479 Once the available evidence has been integrated, gaps in knowledge should be identified. It  
480 may be that these gaps in knowledge should be addressed before the pediatric extrapolation  
481 concept can be finalized. However, gaps in knowledge do not necessarily preclude a pediatric  
482 extrapolation concept from being finalized. The pediatric extrapolation plan should address



483 what data should be collected to fill these gaps in knowledge. Knowledge gap identification  
484 should address the following questions:

485

486 • What are the identified gaps in knowledge?

487

488 • Do these gaps in knowledge require additional data collection before the pediatric  
489 extrapolation concept can be finalized? If so, when and how will these data be  
490 collected?

491

492 • If these gaps in knowledge do not preclude finalization of the pediatric extrapolation  
493 concept, when and how will these gaps in knowledge be addressed in the pediatric  
494 extrapolation plan?

495

### 496 **3.7 Presentation of the Pediatric Extrapolation Concept**

497 Presentation of the pediatric extrapolation concept should include a summary of the overall  
498 similarities between the reference and target populations, the current knowledge gaps, and  
499 limitations of the data. This presentation should include the following:

500

501 • An assessment of the evidence (i.e., overall strengths and weaknesses) of the  
502 similarities and differences between the reference and target population (disease, drug  
503 (pharmacology), response to treatment). This should also include an assessment of the  
504 quantity and quality of evidence.

505

506 • An assessment of the gaps in knowledge and how they affect the confidence and  
507 uncertainties in the extrapolation concept. In addition, the summary should describe  
508 when and how the gaps in knowledge will be addressed.

509

510 • An assessment of the available safety information and how this safety information  
511 affects the extrapolation concept.

512

#### 513 **4. Pediatric Extrapolation Plan**

514 Once a pediatric extrapolation concept has been developed, the relevant study(ies) should be  
515 detailed in the extrapolation plan. The design of the study(ies) should reflect the information  
516 that needs to be collected as presented in the extrapolation concept. The approach can range  
517 from matching effective and safe exposures in the reference population to generating controlled  
518 efficacy and safety data in the target population. The design, timing, analysis, interpretation  
519 and reporting of studies included in the pediatric extrapolation plan are considered below.

520

#### 521 **4.1 Dose Selection**

522 Evaluation and selection of an appropriate dose to be studied is critical to achieve target  
523 exposures and responses. Before initiating pediatric studies, the available scientific information  
524 pertaining to the mechanism of action of the drug, the pharmacokinetics of the drug (ADME),  
525 and the effects of physiologic maturation of any organs and targets that are involved in the  
526 predicted exposures and responses to the drug and/or its active metabolites should be assessed  
527 (see section 3.2). As part of planning for dose selection, other considerations (e.g., safety,  
528 formulation, final dosing regimen) should be incorporated.

529

530 Exposure-response (E-R) relationships developed from data collected in a reference population  
531 can provide a strong pharmacological basis for justification of the exposure(s) ranges to be  
532 targeted. Subsequent simulations, incorporating relevant knowledge and available models, can  
533 be performed to inform dose selection (see section 4.2).

534 It is important to note that the identification of safe and effective dose(s) in the program with  
535 the reference population does not always require or result in the demonstration of an exposure-  
536 response (E-R) curve. As such, there is no requirement to establish an E-R curve in pediatrics.  
537 However, the lack of demonstrable E-R relationship in the reference population or the inability  
538 to demonstrate similar E-R curves in the reference and target populations does not preclude the  
539 use of exposure matching for dose selection purposes in the pediatric extrapolation plan. Dose

540 selection based on exposure matching under such circumstances is reasonable and pragmatic  
541 and is predicated on the expectation that comparable response at the target drug response is  
542 likely to be achieved. Furthermore, there are situations in which randomization of pediatric  
543 patients to subtherapeutic doses may be unethical and available safety data may not support  
544 evaluation of higher doses/exposures.

545 The aim of pediatric dose selection often is to target exposures similar to those known to be  
546 safe and efficacious in a reference population for further evaluation in a pediatric  
547 efficacy/safety study (see section 4.3). In this setting, data in the reference population may be  
548 sufficient to predict doses in the target population. Therefore, separate PK studies may not  
549 always be needed in some age ranges. Confirmatory PK data can be collected as part of the  
550 pediatric efficacy/safety studies with use of sparse PK strategies. However, a separate PK  
551 study should be conducted in certain situations (e.g., drugs with narrow therapeutic range, non-  
552 linear PK, and/or potential differences in the effect of disease on the PK of the drug between  
553 the reference and target populations). Lastly, when PK data are available in an adult reference  
554 population with the disease and the exposure is within an observed exposure range in a  
555 reference pediatric population with a different disease(s), additional PK assessment may not be  
556 necessary in the target population; however, this approach relies on understanding the effect of  
557 disease on the PK of the drug.

558

#### 559 ***4.1.1 When Dose Ranging Data Should be Collected?***

560 Dose ranging data may be needed as part of the pediatric extrapolation plan. Such  
561 circumstances may include when there is uncertainty in the disease similarity and/or response  
562 to treatment; when there are potential age-related differences in target expression; or when  
563 there is lack of correlation between systemic drug exposures and therapeutic response (e.g.,  
564 locally acting drugs). E-R studies can rely on a clinical endpoint or a biomarker response (see  
565 sections 4.3 and 4.1.2). Depending on the biomarker and the time course of the disease, dose-  
566 ranging to achieve different degrees of biomarker/clinical response or an intra-patient dose  
567 titration to a target biomarker effect can be considered.

568

569 **4.1.2 Use of Biomarkers**

570 When available, biomarkers that can be used to support both adult and pediatric development  
571 programs are desirable as are biomarkers that specifically track pediatric disease progression  
572 and/or treatment effect. As an adjunct to the observed biomarker time course, a physiologic  
573 and/or mechanistic representation that describes such data in response to drug therapy is highly  
574 beneficial. Modeling and simulation approaches such as physiologically based  
575 pharmacokinetic (PBPK) modeling and quantitative system pharmacology (QSP) models can  
576 be useful to support the biomarker strategy and choice of clinical endpoints in children.

577

578 A biomarker may or may not need to be validated, although use of a validated biomarker may  
579 require less justification. Methodological considerations (e.g., the effect of missing data, and  
580 the results of sensitivity analyses to departures from any assumptions) should also be included  
581 in the evaluation of the proposed endpoint [see ICH E9(R1)].

582

583 If a biomarker has been proposed for use as a primary analysis in the target population and  
584 cannot be measured in the reference population, relevant clinical outcomes in the target  
585 population should at least be measured as well, to try and understand the relationship between  
586 the variables.

587

588 **4.1.3 Scenarios for Dose Selection**

589

590 **4.1.3.1 When only PK data are Needed to Establish Efficacy**

591 When there is strong evidence 1) to support similarity of disease between the reference and  
592 target population; and 2) that exposures in the reference population will provide similar  
593 response in the target population (e.g., infectious diseases, partial onset seizures); targeting

594 effective exposures in the reference population as the basis for pediatric extrapolation (i.e.,  
595 exposure matching) may be reasonable. Modeling and simulation strategies should be applied  
596 to support the initial dose selection in the exposure matching study in the target population (see  
597 section 4.2). Allometric scaling can be used to account for weight-based changes in clearance  
598 and volume of distribution and maintain consistent exposures across various age/body weight  
599 groups. Models should also take into account other factors that may contribute to variability  
600 in exposures such as maturation. In addition, model-informed dose selection should include  
601 an assessment of the feasibility and practicality of the dosing strategies. For example, fixed-  
602 dose combinations, dose volume constraints, and drug-device combination can influence the  
603 dosing strategy. Once PK data are obtained in the target population, the proposed dosing  
604 regimen should be re-evaluated through simulation techniques before a final dosing regimen  
605 for proposed product labeling is selected.

606

607 *Endpoint: Target exposure metric*

608 When the pediatric extrapolation strategy relies on matching adult exposures, the target  
609 exposure metric(s), range, and acceptance criteria should be prospectively specified and should  
610 be defined in the context of the disease, treatment regimen, route of administration, and  
611 formulation. The target exposure metric should be based on the exposure range associated with  
612 treatment response (efficacy and/or safety) and can be derived from established exposure-  
613 response relationships or observed data in the reference population. The selected target  
614 exposure metric(s) should be associated with the treatment response, and an adequate  
615 discussion and justification should be provided based on, but not limited to, the mechanism of  
616 action and the metrics previously established in the exposure-response relationships in the  
617 reference population. It is often useful to present several exposure metrics. For example,  
618  $AUC_{0-t}$  or  $C_{min}$  may correlate with efficacy whereas  $C_{max}$  may be more informative for safety.  
619 In cases where systemic exposure does not correlate with efficacy (e.g., most locally acting  
620 drugs), additional assessment of response might be needed (see section 4.1.3.2 and 4.3).

621

622 *Sample size*

623 The sample size for a pediatric PK study should be sufficient to meet the objectives of the study  
624 and be based on quantitative methods (modeling and simulation and/or statistical approaches).  
625 Adequate representation of subgroups (e.g., body weight ranges, age ranges) should be  
626 considered and justified. The sample size justification and its feasibility in the targeted  
627 indication should include the following:

628

629 • The availability of patients in a specific body weight/age range

630

631 • The adequacy of the sample size to demonstrate precision in key PK parameters in the  
632 pediatric population such as clearance and volume of distribution

633

634 • The adequacy of the sample size to match the pre-specified target exposure range (e.g.,  
635 the interquartile range for the PK metric(s) in the reference population)

636

637 • The methodology(ies) used to determine the sample size

638

639 Modeling and simulation techniques such as optimal design and/or clinical trial simulation  
640 should be conducted to justify the timing and number of PK samples. The timing of sample  
641 collection should be aligned with clinical care whenever possible [see ICH E11(R1) section  
642 2.4.1].

643

644 *Analysis and reporting*

645 Different presentations of the exposure data in the target and reference populations should be  
646 available to inform regulatory decision making. A single acceptance boundary for all drug  
647 products and drug classes (as compared to bioequivalence testing) will not provide a  
648 meaningful approach in the setting of pediatric extrapolation. An evaluation of confidence  
649 intervals for the mean differences in key exposure metrics such as AUC and C<sub>max</sub> could be an  
650 acceptable approach. The chosen boundaries of the confidence interval should reflect the

651 context of the therapeutic range of the drug and the risk-benefit of the product for a given  
652 pediatric indication.

653

654 A model-based comparison (that can integrate all available data) is generally preferred rather  
655 than a descriptive comparison of observed adult and pediatric exposure data alone. In addition,  
656 inter-individual variability needs to be considered in establishing exposure similarity rather  
657 than comparing means alone. A simulation of the percent of subjects at different age/weight  
658 ranges that lie within (or outside) a pre-defined exposure range may provide a more meaningful  
659 assessment of exposure similarity.

660

661 In general, the most relevant covariate to influence PK in pediatric patients is body weight. In  
662 the youngest pediatric patients (e.g., infants and neonates), in addition to body weight, age is  
663 also an important covariate to account for relevant organ maturation.

664 Relevant predefined exposure metrics should be presented graphically versus body weight  
665 and/or age on a continuous scale. Relevant age and body weight ranges should be depicted in  
666 figures to allow for clear visualization of important covariates (e.g., dose(s), age, weight) as  
667 well as in tabular format. The reference range in the adult population (e.g., median and outer  
668 percentiles of the distribution of observed or simulated data) should also be presented  
669 graphically and in tabular format.

#### 670 ***4.1.3.2 When Effect on a Biomarker is Needed to Establish Efficacy***

671 When exposure matching alone is insufficient to establish efficacy, biomarkers can be used as  
672 part of the extrapolation plan. In this situation:

673

- 674 • Use of a validated biomarker as a surrogate endpoint is recommended but not required.
- 675
- 676 • The choice of the biomarker endpoint should be supported by available data in the  
677 reference and target populations and justified in the extrapolation plan.

678

679       • A biomarker on the causal pathway that is correlated with clinical efficacy in the  
680       reference population is often acceptable and should be justified also with regard to its  
681       relevance to the target population.

682

683       • Models can be used to estimate the quantitative relationships between biomarkers and  
684       clinical efficacy (see section 3.6).

685

686 In order to rely on the use of dose/exposure to achieve a biomarker effect, it is important to  
687 have confidence that there is a relationship between the biomarker effect and efficacy in the  
688 reference population. Models could investigate the mechanistic basis for selected biomarkers,  
689 facilitate the analysis of biomarker data, and optimize the data collection needed to support  
690 and/or confirm the relationship between the biomarker and efficacy in the reference population  
691 (see section 4.2).

692

### 693 *Sample size*

694 Quantitative methods (modeling and simulation or statistical approaches) should be used to  
695 derive sample size for PK/biomarker and biomarker endpoints. The sample size for the study  
696 can vary depending on variability in key drivers such as PK and PK/PD. Consideration of the  
697 timing and number of data points per subject for both PK and PK/PD should determine the  
698 appropriate sampling.

699

### 700 *Analysis and reporting*

701 The data used in the analysis should be described, with a focus on the important elements  
702 relevant to the objectives of the analysis, i.e., the comparison between the biomarker effect in  
703 the target population and that in the reference population. A therapeutic range of the biomarker



704 effect that provides a meaningful assessment of similarity between the reference and target  
705 populations should be pre-defined.

706

707 Results should be summarised with adequate graphical and tabular displays, e.g., illustrative  
708 plots for clinical interpretation. The clinical relevance of the results should be discussed,  
709 including the impact of any sensitivity analyses (see section 4.1.3.1 *Analysis and reporting*).  
710 The analysis and reporting should confirm a dose-exposure-response relationship that  
711 establishes the effective dose(s).

712

#### 713 **4.1.4 Other Considerations**

714 As has been emphasized through this guideline, pediatric extrapolation should be considered  
715 as a continuum. Because of this continuum, there can be some overlap in the types of  
716 extrapolation plans that are developed. For example, an extrapolation plan can include a  
717 scenario that only requires collection of PK in the target population as the primary objective  
718 but additional secondary clinical outcome measures can be included in order to increase  
719 confidence with the “PK-only” approach. There can also be some overlap between the design  
720 of a single-arm PK/PD study and a single-arm, uncontrolled study that relies on a clinical  
721 efficacy endpoint (see section 4.3.1). Ultimately, the specific study designs used in any  
722 extrapolation plan should be justified based on the extrapolation concept and discussed with  
723 regulatory authorities.

724

#### 725 **4.2 Model-Informed Approaches**

726 Modeling and simulation approaches are powerful tools that can be used, for example, to  
727 examine and inform study design, derive dosing recommendations, or perform sensitivity  
728 analyses. Quantification of relevant relationships (e.g., dose-exposure, exposure-response)  
729 provides an important foundation to conduct simulation in support of the dose selection. In  
730 addition, simulations of therapeutic window(s) associated with relevant PK or PK/PD

731 endpoints can be explored prior to conducting a pediatric study. Modeling and simulation can  
732 be used to validate the pediatric extrapolation concept after completion of the pediatric study.  
733 When simulations are used for regulatory decisions, it is important to provide information that  
734 the models are fit for simulation purposes and that model assumptions and the simulation set  
735 up are clearly reported. Typically, this information would be provided in the form of a modeling  
736 and simulation plan that the sponsor generates for internal documentation purposes but is also  
737 suitable for interaction with regulators.

738

739 The availability of the various data sources dictates, in part, the methodologic approach with  
740 more top-down approaches (e.g., traditional PK/PD, population-based PK/PD) reliant on adult  
741 data and bottom-up approaches (e.g., PBPK, QSP) dependent on physicochemical, *in vitro* and  
742 preclinical *in vivo* data. For ADME prediction, data of interest include the physicochemical  
743 properties of the drug, *in vitro* data describing individual PK attributes, PK/PD data from  
744 preclinical *in vivo* experiments, and any PK/PD data from adults.

745

746 When using existing models (e.g., population PK, PBPK, population PK/PD models), the  
747 specific characteristics of the target population, such as relevant body size and organ  
748 maturation, should be incorporated in the model. Depending on the available data and goals of  
749 the modeling, there are several techniques that can be used to incorporate information from the  
750 reference population in the analysis of the target population; for example, using models based  
751 on the reference population, analysis with pooled datasets, or Bayesian approaches with prior  
752 distributions for model parameters.

753

754 When making model-based assessments, the components of the model may have complex  
755 interrelationships (e.g., correlation of parameters and/or assumptions) that should be captured  
756 in the structure of the model along with any time dependencies. These features should be  
757 incorporated into the model at inception. Model equations and assumptions underlying the

758 model structure or dataset need to be clearly presented so that their relevance to the overall  
759 strategy, model predictions and elements of uncertainty can be properly assessed. Not all data  
760 and model elements are equally valuable; therefore, assumption testing is an important aspect  
761 of any extrapolation exercise and should be integrated into the analysis plan and report. Given  
762 the scope of model assumptions, there should be multidisciplinary input to fully evaluate the  
763 assumption-testing exercise.

764

765 It is important to distinguish between different sources of uncertainties and variance. For  
766 example, there is inherent variability in samples taken between individuals (i.e., between  
767 subject variability), which is a biological phenomenon and the magnitude of which can be  
768 directly supported by data. There is also uncertainty in model parameters which cannot be  
769 measured directly but are influenced by data content, or lack thereof. Collecting additional data  
770 can help improve the precision of these estimates. There are also parameters that should be  
771 specified where there is more limited or no data to support values chosen, and there is a degree  
772 of arbitrariness in their choice which is inherently uncertain. All of these can contribute to  
773 overall uncertainty in the results, and the different contributions that these could have should  
774 be addressed and justified during the exercise.

775

### 776 **4.3 Efficacy Studies**

777 When clinical studies are required in order to generate efficacy data in a pediatric extrapolation  
778 plan, one of the most important design decisions will be the choice of control arm. The options  
779 may include a randomised concurrent control, a formal statistical comparison against an  
780 external control, or a single arm trial. The choice will be influenced by the scientific question(s)  
781 identified in the pediatric extrapolation concept.

782

783 **4.3.1 Single Arm Efficacy Studies**

784 In some situations, single arm studies may be the most appropriate way of generating the  
785 required evidence. This would be the case, for example, when the standard of evidence in the  
786 reference population is a single arm trial. When designing the study, how the primary efficacy  
787 objective would be evaluated should be defined using a pre-specified threshold.

788

789 The sample size of studies should be calculated to ensure the threshold is met, or to ensure that  
790 an estimate of sufficient precision is obtained. External data can be used to contextualise the  
791 results (e.g., using published literature to understand the context of the results of the study with  
792 respect to current clinical practice, but without requiring a formal comparison of efficacy to  
793 external data).

794

795 **4.3.2 Externally Controlled Studies**

796 It may be possible and appropriate in some circumstances to use external data as the formal  
797 comparator in a trial. This could be from the comparator arm in the reference population,  
798 relevant control arms from other randomized controlled trials (RCTs), or real-world evidence  
799 sources in the target population. Using external data beyond these sources, e.g., from different  
800 pediatric populations, different diseases or where different endpoints are used, is more  
801 challenging and should be justified.

802

803 As with any other study without randomized concurrent control, drawing causal inferences is  
804 more challenging. Since the data are compared directly with a data source external to the study,  
805 appropriate statistical methods should be used to account for differences between the  
806 populations. It is important to reflect that these studies would still be controlled, albeit with a  
807 non-randomized control, which differs from the approach of just comparing to a threshold.

808

809 **4.3.3 Concurrent Controlled Efficacy Studies**

810 In some situations, the data generated to date and the outputs of the pediatric extrapolation  
811 concept are such that randomized controlled efficacy studies would be needed as part of the  
812 pediatric extrapolation plan to be able to draw benefit risk conclusions. Based on the pediatric  
813 extrapolation concept, the need for controlled studies and the ability to extrapolate leads to  
814 study designs different than those that were required in the reference population. This will lead  
815 to a different relationship between the false positive rate, the false negative rate and sample  
816 size that is not the same as it is in the reference population. When the sample size is limited,  
817 the relative importance of false positive and false negative results should be considered  
818 carefully.

819

820 It follows that extrapolation options may comprise many different design options that can be  
821 used to generate data, but not according to the traditional approach (e.g., p-value less than 0.05  
822 generated in a frequentist fashion from an RCT). The extrapolation approach will result in a  
823 sample size smaller than one would expect for a standalone efficacy study. If the study is  
824 powered to meet a relaxed success criterion with a significance threshold larger than 0.05, this  
825 should be justified in advance.

826

827 An alternative approach for active controlled trials may be to maintain the conventional type I  
828 error rate but widen the non-inferiority margin usually used in *de novo* adult development,  
829 especially when the aim is not to demonstrate efficacy *per se* but to demonstrate that efficacy  
830 is in line with prior expectations based on the extrapolation concept. It will be important to  
831 ensure the point estimate obtained should be consistent with that in the reference population.

832

833 **4.3.4 Incorporation of External Data**

834 When identifying which information will be incorporated into the analysis of the pediatric  
835 study, relevant data should be identified through a systematic search using pre-specified

836 selection criteria. Ideally, the sources of information to be leveraged should be agreed upon  
837 with regulatory authorities ahead of time. However, it is possible that the external data  
838 themselves may not be available yet, for example, if generated from trials running in the  
839 reference population in parallel to the study in the target population or borrowed across age  
840 groups in the same study.

841

842 The types of information that could be leveraged in an analysis include individual patient data  
843 and/or aggregate data from other sources. Having access to individual patient data in the  
844 reference population enables comparison of the distribution of baseline prognostic factors with  
845 the target population. Potential differences between the study from which the reference data  
846 will be derived and the data generated in the target population can be adjusted and accounted  
847 for in the analysis as much as possible.

848

#### 849 ***4.3.5 Quantifying the Impact of Use of Reference Data***

850 It is important to understand *a priori* how much available information is being incorporated  
851 into the design and analysis to support the interpretation of the pediatric trial. In particular, it  
852 is of relevance to know how much of the data that has been generated in the reference  
853 population is being used in the exercise, but also how much of the data generated in the  
854 reference population is relative to the amount of data generated in the target population. If the  
855 available information (based on reference data, or outputs from a modeling and simulation  
856 exercise) is summarised as a statistical distribution then the effective sample size is a good way  
857 of describing how much information is being used.

858

859 If Bayesian approaches are used, different ways of using the prior information, for example by  
860 using a mixture prior or power prior, will have a different effective sample size depending on  
861 the choice of parameters used in the model. If such strategies are employed, sensitivity analyses  
862 looking at the effective sample size under different values of these parameters will better help

863 understand the design properties. Regardless of the approach used, the method of borrowing  
864 proposed should be pre-specified and sensitivity analyses to understand the effect on operating  
865 characteristics of different amounts of borrowing will better help understand the design  
866 properties.

867

868 Sometimes it may not be appropriate to use the reference data as is, and the data should be  
869 modelled to match the target population more closely. This will be the case when there exist  
870 known differences in the disease (e.g., severity) that can be quantified and predicted based on  
871 measured covariates, though the extrapolation concept is still applicable. In other situations,  
872 there exist known differences in study design (e.g., the endpoint measured is different in the  
873 target population or the endpoint is measured at a different time) though the disease is  
874 considered to be similar to a degree that allows extrapolation. How the reference data are used  
875 in this situation would have to be considered on a case-by-case basis depending on the degree  
876 of similarity of disease, drug pharmacology, and response to treatment.

877

878 It can be possible to base a pediatric extrapolation plan using a biomarker, surrogate endpoint,  
879 or clinical endpoint as the primary endpoint in the target population, even if it is not the primary  
880 endpoint in the reference population [see ICH E11(R1) section 5.1.1]. In this scenario, an  
881 evaluation of the robustness of the correlation of the proposed endpoint to the primary efficacy  
882 endpoint in the reference population should be conducted. Where relevant, it may be prudent  
883 to initiate the evaluation of potential pediatric endpoints as part of the adult development  
884 program prior to their incorporation into the pediatric program.

885

#### 886 ***4.3.6 Presentation and Justification for the Pediatric Trial***

887 Diagrams that represent the overall planned trial design for the extrapolation plan are helpful,  
888 especially if the design is complex. This may be the case if, for example there is an adaptive  
889 design, or a trial with multiple stages evaluating different aspects of clinical development in

890 each stage. When evaluating a trial design, determining what potential results will lead to a  
891 successful study based on pre-defined criteria can help to understand what magnitude of  
892 treatment effect would need to be observed for a trial to be declared a success. Tables or plots  
893 of different critical thresholds could be useful if there is uncertainty around the most  
894 appropriate threshold.

895 If a Bayesian design is used, the full operating characteristics should be provided. Additionally,  
896 the results of an analysis of the data alone should always be provided.

897

#### 898 ***4.3.7 Analysis, Reporting, and Interpretation***

899 If a frequentist design is used, an alternative threshold to cross other than the standard two-  
900 sided significance level of 5%. should be agreed upon in advance and a frequentist analysis  
901 compared to this alternative threshold provides a justification of the pediatric extrapolation  
902 concept. If the endpoint is the same in the reference population as the target, ideally the same  
903 analysis method should be used in the target population as in the reference population. A  
904 frequentist meta-analysis approach combining reference and target data could be conducted if  
905 it is appropriate to formally analyze the data together.

906

907 If a Bayesian design is used, which explicitly leverages external data, there are many more  
908 choices to be made for the analysis. This analysis should be pre-specified and updated as data  
909 are generated. Visualisations to better understand the relationship between operating  
910 characteristics and underlying parameters and assumptions are helpful. Plots of posterior  
911 distributions resulting from Bayesian analyses may better contextualize the summary statistics  
912 derived from Bayesian distributions. If data external to the trial are incorporated into the  
913 analysis, the reporting should explicitly describe this and discuss how and when these data  
914 were originally generated and where they were reported, along with a justification as to why  
915 they are considered to be appropriate to include.

916



917 Ideally, the interpretation of a study is aided if the success criteria are described and agreed  
918 upon in advance with Regulatory Agencies. The criteria for success can be a p-value, or if  
919 reference data are explicitly borrowed, Bayesian success criteria, such as credible intervals,  
920 excluding critical values, or the probability that one treatment is better than the other by at least  
921 a certain pre-specified amount. More than one success criterion may be appropriate. For  
922 example, if a non-inferiority margin wider than would be accepted in adults is used, it is also  
923 possible to specify the point estimate of treatment effect that would need to be demonstrated  
924 for non-inferiority to be met for any given sample size and variance. This could help in  
925 demonstrating efficacy by providing additional reassurance of the expected treatment effect. It  
926 is important to understand how similar the target data are to the reference data and to use  
927 metrics to define such similarity. If the observed data in the study are not similar to the observed  
928 reference data, this may limit the applicability of the pediatric extrapolation concept and the  
929 amount of data that may be considered reasonable to borrow.

930

931 Nevertheless, if the data in the target population is substantially better than the reference  
932 population in terms of the point estimate of effect, but statistical significance without  
933 borrowing has failed to be achieved due to a small sample size, it may be of interest to  
934 understand how much weight needs to be put on this reference data before a positive conclusion  
935 is drawn (i.e., using a tipping point analysis).

936

937 The more complex a statistical model, and the more parameters that need to be assumed, the  
938 greater the need for appropriate and wider ranging sensitivity analyses [ICH E9 (R1)]. It is  
939 beneficial to discuss these sensitivity analyses in advance, and to investigate how robust the  
940 interpretation of the primary analysis might be to changes in these parameters. Such analyses  
941 should be carefully selected to investigate the assumptions made with the primary estimator  
942 and other limitations with the data.

943

944 *Methods of leveraging source data in the analysis of a pediatric trial*

945 When deciding on the method to use, simulation can be a useful tool to inform the choice of  
946 analysis strategy, with a view to optimizing the trade-off between bias, power, and type I error  
947 rate control. Various methods exist that aim to limit the borrowing if the data generated are  
948 not similar to the prior belief about them. As an example, one possible method amongst many  
949 is to use a robust prior: a two-component mixture prior where one component is an informative  
950 prior based on the source data and the second is a weakly informative prior independent of the  
951 source evidence. The weakly informative component should be carefully chosen to ensure  
952 adequate borrowing behavior. The prior weight attributed to the informative component of the  
953 mixture prior can be considered as the prior belief about the plausibility and acceptability of  
954 the extrapolation concept. The closer the value to 1, the more confidence there is. If small  
955 changes in the pre-specified parameters such as the weighting parameter above, lead to large  
956 changes in the operating characteristics of the study, the method may not be sufficiently robust.

957

958 A sensitivity analysis such as a tipping point analysis can be a useful tool for retrospectively  
959 assessing the robustness of conclusions to the strength of prior assumptions about similarity of  
960 source and target population parameters. When source data are drawn from several different  
961 sources, such as adult RCTs, epidemiological studies or registry data, the quality of data from  
962 the various sources may differ, and their relevance to the new pediatric trial may differ. In this  
963 case, careful consideration should be given to both the construction of the prior itself, and the  
964 method used to include the data in the analysis.

965

966 **5. Additional pediatric extrapolation plan considerations**

967

968 **5.1 Safety Plan**

969 As described above, the extrapolation concept should include a discussion of the extrapolation  
970 of safety and a thorough justification to support any conclusions about the acceptability to

971 extrapolate safety information from the reference to the target population (see section 3.5). The  
972 approach to safety data collection should reflect the scientific question(s) that needs to be  
973 answered, the knowledge gaps identified, and the uncertainties that are being addressed to  
974 support the safety of the drug in the target population. Even when extrapolation of safety data  
975 is justified, there may be additional safety issues that should be addressed. A comprehensive  
976 safety plan, including the need for pre- and post-marketing safety data collection should be  
977 described in the extrapolation plan.

978

## 979 **5.2 Inclusion of Adolescents in Adult Trials**

980 The enrollment of adolescents into adult clinical trials may hasten adolescent access to safe  
981 and effective treatments as well as accelerate the gathering of needed pediatric data.  
982 Historically, pediatric trials have not been initiated until after adult development has been  
983 completed and/or after the drug has been approved for adults. As a result, enrollment into  
984 pediatric trials may be slow due to the off label pediatric use of the drug, further delaying  
985 broader pediatric and adolescent access to effective treatments. Inclusion of adolescents in  
986 some disease- and/or target-appropriate adult trials may address this problem. If the adolescent  
987 results are used to bridge the extrapolation of adult efficacy and/or safety to younger children,  
988 the similarity of disease and response to treatment between the younger children and  
989 adolescents, and any uncertainties, should be addressed.

990

991 The decision to include a pediatric cohort (e.g., an adolescent subgroup 12 to 17 years of age)  
992 in an adult (e.g., > 18 years of age) clinical trial assumes the disease and response to treatment  
993 are sufficiently similar between the adolescent and adult patients. As such, the objective(s) of  
994 including adolescents and adults in a single trial should be framed within the context of the  
995 extrapolation concept. Additional data to inform adolescent dosing may not be necessary as the  
996 adolescent and adult PK are generally similar. In such situations, specific consideration  
997 pertaining to the impact of lower body weight in adolescents should be carefully considered.

998

999 If the disease and response to treatment are sufficiently similar, the adolescent and adult  
1000 populations can be combined into a single analysis of efficacy. The purpose and statistical  
1001 methods for a separate analysis of the adolescent subgroup need to be carefully considered so  
1002 that any identified differences or uncertainties are addressed. Such subgroup analyses should  
1003 be interpreted cautiously; the strength of any conclusion about the extrapolation of efficacy (or  
1004 lack thereof) based solely on exploratory subgroup analyses may be limited (see ICH E9).

1005

1006 There may be ethical and operational challenges associated with including adolescents in an  
1007 adult trial, such as: (1) different standards for the acceptable balance of risk and potential  
1008 benefit; (2) whether adolescents should be exposed to a placebo control (which may be used  
1009 more often in an adult trial); (3) the need for parental permission in addition to adolescent  
1010 assent; (4) the use of the same primary endpoint in both the adolescent and adult population;  
1011 (5) the need for pediatric-specific study sites; and (6) the willingness of pediatric investigators  
1012 to participate in a subsequent pediatric only trial that would now exclude adolescents. If  
1013 confronted with these challenges, different trial designs can also be considered (such as an  
1014 adolescent trial run in parallel to the adult trial). Nevertheless, when the disease and response  
1015 to treatment are sufficiently similar between adolescent and adult subjects, there should be a  
1016 strong justification for why adolescents are not being included in an adult clinical trial or being  
1017 studied in a parallel trial.