E11A Pediatric Extrapolation

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For questions regarding this draft document, contact (CDER) Lynne Yao, (301) 796-2141.

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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

ICH HARMONISED GUIDELINE

PEDIATRIC EXTRAPOLATION

E11A

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ICH Consensus Guideline

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1. Introduction

1.1. Objectives of the Guideline

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

1.2. Background

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

Historically, extrapolation of safety generally was considered unacceptable. However, our understanding of similarities and differences between reference and target populations with respect to safety has evolved. As described in the ICH E11(R1) guideline, the principle of using data generated in a reference population to define the scope and extent of data that should be collected in a target population can also apply to the generation of safety data (see section 3.5).

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

1.3. Scope

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

The guideline discusses how the use of statistical and other quantitative tools (e.g., modeling and

[1] For the purposes of this document "disease" includes both "diseases" and "conditions"

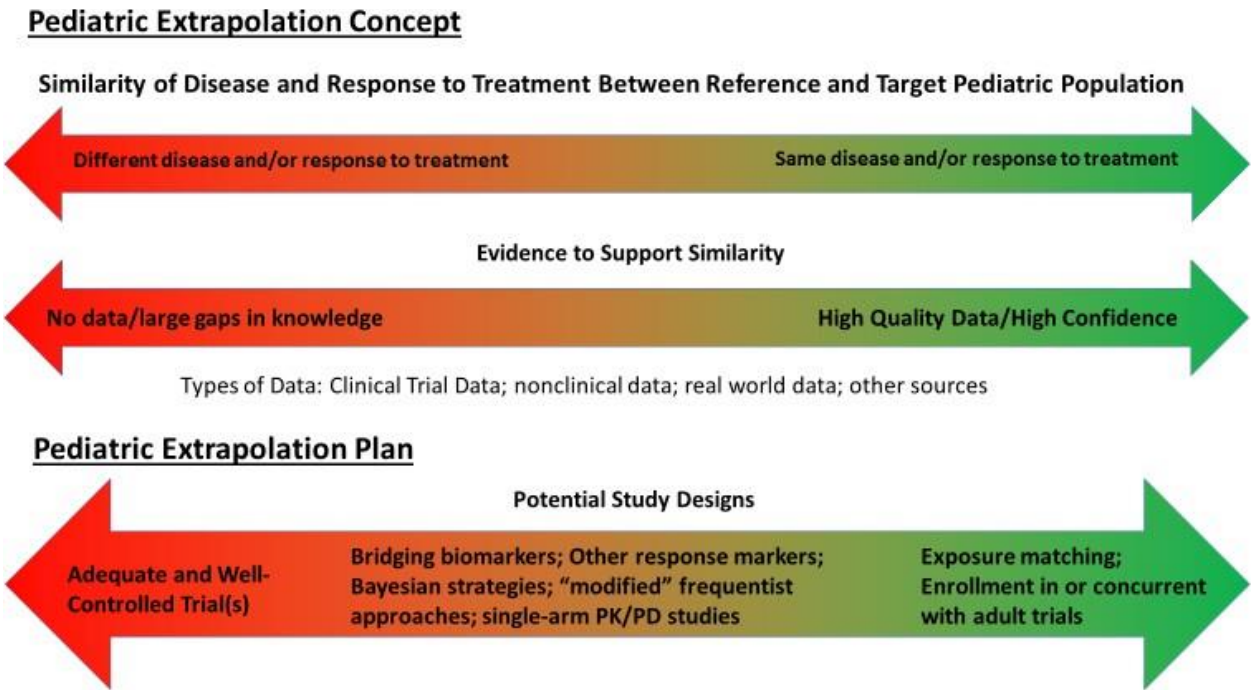
simulation) can be leveraged to fill in gaps in knowledge. This guideline is not intended to provide a comprehensive listing of all the situations where extrapolation of data can play an important role in pediatric drug development, but it does explain how pediatric extrapolation can be applied practically to support the safety and efficacy of a product in pediatric populations. This guideline does not discuss other types of "extrapolation" – for example, the ICH E5 guideline should be consulted regarding the concept of "bridging studies" to leverage foreign clinical data from one region for extrapolation to another region's population as a basis for registration of a medicine. Although there are some quantitative strategies mentioned or explained within the guideline, it is not meant to be a comprehensive instruction guide. Some basic understanding of the role of quantitative approaches used in clinical trial development is expected.

1.4. General concepts

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

In the ICH E11(R1) definition of pediatric extrapolation, "sufficiently similar" might suggest a threshold that must be exceeded for pediatric extrapolation to be acceptable for regulatory consideration. However, whether the course of disease and expected response to treatment can be considered sufficiently similar between a target and reference population is not simply a "yes or no" question. Therefore, this guidance does not use discrete categories (e.g., full, partial or none) to describe the different approaches to pediatric extrapolation, in favour of identifying the clinical trial designs which can address the remaining uncertainties based on an assessment of the existing data. The use of extrapolation as discussed in this guideline reflects that a continuum of dissimilarity/similarity may exist. There may be uncertainties associated with the data supporting extrapolation to the target pediatric population. The extrapolation approach should address these uncertainties, utilizing clinical judgement to establish the tolerable level of uncertainty (see Figure 1). Options for trial designs will depend on the level of uncertainty that needs to be resolved.

Figure 1: Pediatric Extrapolation Approach



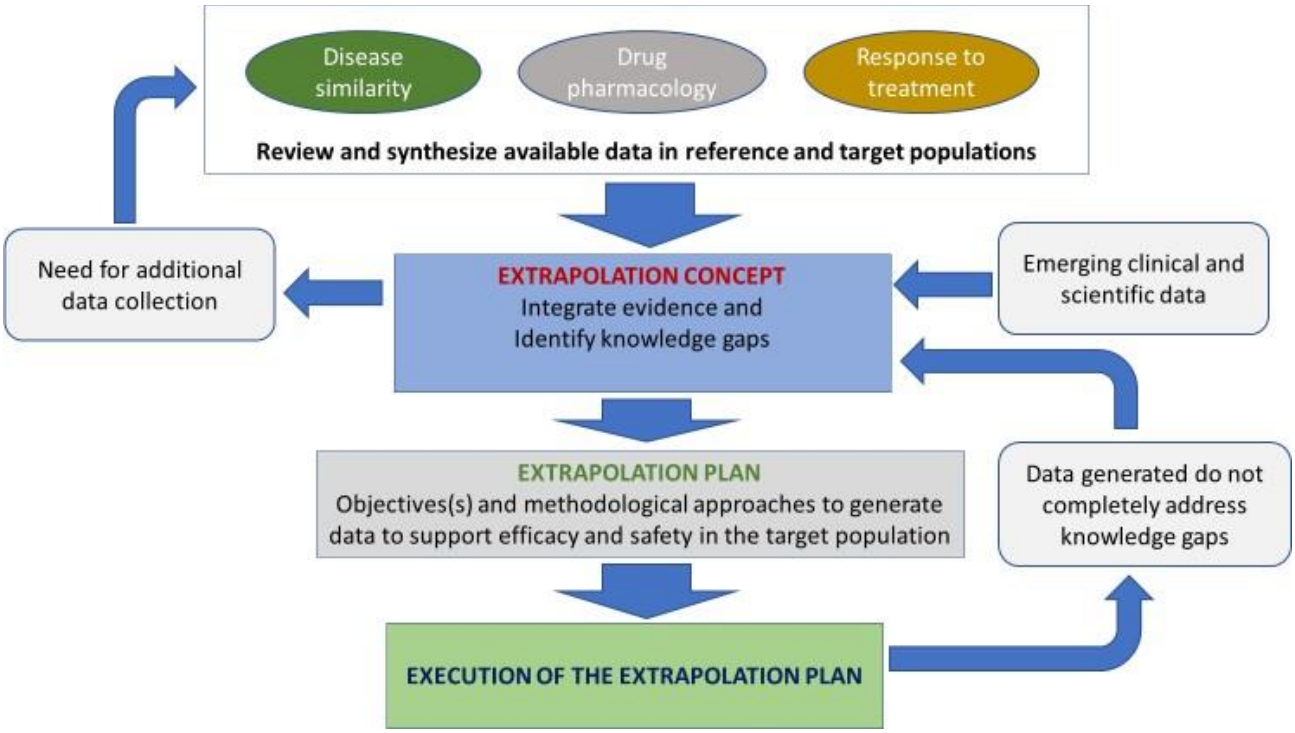
2. Pediatric Extrapolation Framework

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

The first step is the development of a pediatric extrapolation concept. The concept is developed through comprehensive and detailed review of existing information about the range of factors that define the disease, the drug pharmacology, and the clinical response to treatment across the reference and target populations. Factors that influence the effects of treatment in the reference and target populations should be identified. Once a review of the existing knowledge has been conducted, the data should be synthesized to develop the pediatric extrapolation concept. Methods to review and synthesize these data can include quantitative approaches such as statistical methods and modeling and simulation. Synthesis of the data should be conducted to both understand the strength of the known data as well as to identify important gaps in knowledge which will inform what additional data, if any, are required.

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

Figure 2: Pediatric Extrapolation Framework



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

3. Pediatric Extrapolation Concept

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

3.1. Disease Similarity

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

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

It can also be possible to identify disease subgroups in both the reference and target populations

that are sufficiently similar to support the use of pediatric extrapolation even if the disease in the overall population is not sufficiently similar. For example, anatomic congestive heart failure in children is not similar to adult heart failure, whereas heart failure due to dilated cardiomyopathy is similar between adult and pediatric populations, allowing for extrapolation from adult to pediatric patients with dilated cardiomyopathy.

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

3.1.1.Factors to Consider in the Evaluation of Similarity of Disease

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

Pathophysiology of disease

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

Disease definition

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

- What are the manifestations or diagnostic criteria that define the disease?
- How similar are the manifestations between the reference and target pediatric populations?
- How are the manifestations measured?
- Are there similar measurements used to define manifestations of the disease in the reference and target pediatric populations?
- Are there subtypes (e.g., based on severity, genetics, molecular markers, etc.) of the disease that occur in the reference or target populations?
- What are the similarities and differences in the subtypes of the disease in the reference and target population?
- Are there other factors to consider (e.g., genetic/epigenetic, etc.) that are needed to define the disease?

Course of disease

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

- What are the similarities and differences of the clinical course of the disease between the reference and target populations? Are there differences in the course of the disease based on factors such as the age of onset of the disease?
- Are there similar endpoints and/or biomarkers available that help to measure progression of disease in both the reference and target populations?
- Are the short-term or long-term outcomes of the disease similar for the reference and target pediatric populations and can these outcomes be measured similarly?
- Are there available treatments being used for both reference and target populations?
- What effect have these treatments (e.g., timing of treatment relative to onset of disease and age of the patient, frequency of treatment, length of treatment) had on the course of the disease in the reference and target populations?

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

3.2. Drug (Pharmacology) Similarity

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

Differences in ADME processes can result in differences in pharmacokinetic (PK) parameters and resulting drug exposure. Exposure is a broad concept, ranging from measurement of the systemic (or other biological compartment) exposure of the drug (parent and/or metabolite(s)), at a single point in time (for example maximum or trough concentration), exposure over a time interval (for example AUC0-t or average concentration), or characteristics of the overall concentration-time curve (e.g., clearance, volume of distribution). In addition, differences in MOA properties can result in differences in an exposure-response (E-R) relationship between the reference and target population. Changes in these characteristics over time due to developmental maturation should be considered.

3.3. Similarity of Response to Treatment

As with similarity of disease, the similarities, and differences in response to treatment between a

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

3.3.1. Factors to Consider in the Evaluation of Similarity of Response to Treatment

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

Pharmacokinetics and pharmacodynamics (PK/PD)

The potential effect of developmental and maturational changes on the PK/PD relationship and clinical response should be evaluated. An understanding of the drug target and its role in normal development, disease pathology and expected response to therapy should be evaluated. For example, if a receptor does not exist in the first 6 months of life, no response to treatment would be expected for a drug only targeting this receptor in this age group. Factors that impact response that may differ between the reference and target populations (e.g., concomitant medications, comorbid disease, organ function, genetic makeup) should be evaluated to assess whether there is an impact on the extent to which pediatric extrapolation can be applied.

Response endpoint(s):

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

- How is a response endpoint (e.g., clinical, biomarker, composite, etc.) measured in the reference and target populations?
- Is there a similar measurement of the endpoint used in both the reference and target populations?
- If the response endpoint or measurement of the endpoint is different in the reference and target populations, what is the relationship between the endpoints (e.g., clinical endpoint in the reference population in relation to a biomarker endpoint in the target population)?

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

3.4. Sources and Types of Existing Data

Use of existing data should be fit-for-purpose (i.e., the context in which it was generated is applicable to the context in which it is intended to be used). It is important to consider both the

quantity and quality of data to evaluate the similarities and differences between the reference and target populations. All available data should be used to establish the extrapolation concept and formulate the extrapolation plan. Such information may also include data from ongoing adult/pediatric development programs, or relevant data from terminated programs. Examples of the sources and types of data that should be evaluated are included in Table 1 and are discussed further in this section. Given the considerable overlap in the data used to support similarities and differences in disease, pharmacology, and response to treatment, the sources of data are combined in Table 1.

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

Sources of Data	Types of Data
Clinical data	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
Nonclinical data	ADME Data from animal models
	In silico, *in vitro*, and *in vivo* data (e.g., disease-response, PK, PK/PD, semi-mechanistic, and mechanistic)
	Juvenile nonclinical toxicology data
Real World Data	Data including but not limited to disease registries (regional, national, and international), electronic health records, health claims databases
Other sources	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

Clinical data

Clinical data (e.g., from controlled trials, prospective observational studies, PK, PK/PD and/or biomarker studies) in populations with the same condition or related conditions should be

evaluated to understand similarities and differences between the reference and target populations. All available data for the drug/drug class should be evaluated including ongoing and completed studies, published or unpublished, whether results are positive or negative.

Nonclinical data

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

Real world data (RWD)

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

Other sources

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

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

3.5. Safety Considerations in the Extrapolation Concept

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

3.5.1. Extrapolation of Safety

The principles underlying the appropriate use of data generated in a reference population(s) to define the scope and extent of efficacy data that needs to be collected in a target population can also apply to the generation of safety data (see section 1.2). Extrapolation of safety data could be

considered based on the available knowledge of the known and/or potential safety issues in the reference population that are relevant to the target pediatric population. Other information (e.g., nonclinical, mechanistic) should be considered as part of this analysis. These data should help increase certainty about the expected safety profile of a drug in a particular pediatric population and determine if additional gaps in knowledge need to be addressed in the pediatric program. Evaluation of the suitability and extent to which safety will be extrapolated should be included in the extrapolation concept and plan.

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

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

- What is the age-range of pediatric patients to be studied as part of the safety extrapolation?
- What amount/quality of safety data is available from the reference population?
- Are there known on- or off-target effects of the investigational drug relevant to pediatric safety?
- Are data needed to account for age-specific short- and longer-term adverse effects in pediatric populations, which may not have been identified in studies in the reference population?
- How does the expected treatment duration and treatment effect size in the reference population compare with the target pediatric population?
- How do the expected drug exposures in the reference and target pediatric populations compare? Does the exposure needed to target a specific PD effect or clinical response predict a specific toxicity in the target pediatric population?
- What information is already known from non-clinical (including mechanistic, in vitro, in-vivo) sources that can be leveraged to the target population?
- Are there other differences between the reference and target population that could limit the extrapolation of safety (e.g., a background therapy used in a target population that may potentiate a safety signal but is not used in the reference population)?

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

3.5.2.Additional Safety Considerations

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

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

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

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

3.6. Integration of Evidence and Development of the Pediatric Extrapolation Concept

The goal of the development of the pediatric extrapolation concept is not only to determine whether pediatric extrapolation can be used, but also to describe assumptions made, detail any gaps in knowledge, and assess the impact of uncertainties in the available evidence. This section provides guidance on the review, synthesis, and presentation of information that should be included in a pediatric extrapolation concept.

Integration of existing evidence

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

- What is the body of evidence and what is the clinical relevance of the evidence?
- What are the strengths and the limitations of the evidence?
- How consistent are the findings across the sources and types of data?
- What differences exist in the data and how do these differences affect assessment of similarity?

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

Methodologies that can be used to integrate evidence

Quantitative synthesis of existing data should be used to integrate the evidence (see section 4.2). Use of mechanistic and/or empirical approaches in the synthesis of data should be considered.

Inclusion of systems biology/pharmacology data from the reference population(s) should be considered when population-level data (epidemiological, diagnosis and non-interventional study data) are available. Meta-analytic techniques for synthesizing efficacy data in the reference population(s) should also be considered.

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

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

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

Knowledge gap identification

Once the available evidence has been integrated, gaps in knowledge should be identified. It may be that these gaps in knowledge should be addressed before the pediatric extrapolation concept can be finalized. However, gaps in knowledge do not necessarily preclude a pediatric extrapolation concept from being finalized. The pediatric extrapolation plan should address what data should be collected to fill these gaps in knowledge. Knowledge gap identification should address the following questions:

- What are the identified gaps in knowledge?
- Do these gaps in knowledge require additional data collection before the pediatric extrapolation concept can be finalized? If so, when and how will these data be collected?
- If these gaps in knowledge do not preclude finalization of the pediatric extrapolation concept, when and how will these gaps in knowledge be addressed in the pediatric extrapolation plan?

3.7. Presentation of the Pediatric Extrapolation Concept

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

- An assessment of the evidence (i.e., overall strengths and weaknesses) of the similarities and differences between the reference and target population (disease, drug (pharmacology), response to treatment). This should also include an assessment of the quantity and quality of evidence.
- An assessment of the gaps in knowledge and how they affect the confidence and uncertainties in the extrapolation concept. In addition, the summary should describe when and how the gaps in knowledge will be addressed.
- An assessment of the available safety information and how this safety information affects the extrapolation concept.

4. Pediatric Extrapolation Plan

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

4.1. Dose Selection

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

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

It is important to note that the identification of safe and effective dose(s) in the program with the reference population does not always require or result in the demonstration of an exposure-response (E-R) curve. As such, there is no requirement to establish an E-R curve in pediatrics. However, the lack of demonstrable E-R relationship in the reference population or the inability to demonstrate similar E-R curves in the reference and target populations does not preclude the use of exposure matching for dose selection purposes in the pediatric extrapolation plan. Dose selection based on exposure matching under such circumstances is reasonable and pragmatic and is predicated on the expectation that comparable response at the target drug response is likely to be achieved. Furthermore, there are situations in which randomization of pediatric patients to subtherapeutic doses may be unethical, and available safety data may not support evaluation of higher doses/exposures.

The aim of pediatric dose selection often is to target exposures similar to those known to be safe and efficacious in a reference population for further evaluation in a pediatric efficacy/safety

study (see section 4.3). In this setting, data in the reference population may be sufficient to predict doses in the target population. Therefore, separate PK studies may not always be needed in some age ranges. Confirmatory PK data can be collected as part of the pediatric efficacy/safety studies with use of sparse PK strategies. However, a separate PK study should be conducted in certain situations (e.g., drugs with narrow therapeutic range, non-linear PK, and/or potential differences in the effect of disease on the PK of the drug between the reference and target populations). Lastly, when PK data are available in an adult reference population with the disease, and the exposure is within an observed exposure range in a reference pediatric population with a different disease(s), additional PK assessment may not be necessary in the target population; however, this approach relies on understanding the effect of disease on the PK of the drug.

4.1.1. When Dose Ranging Data Should be Collected?

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

4.1.2. Use of Biomarkers

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

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

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

4.1.3. Scenarios for Dose Selection

4.1.3.1. When only PK data are Needed to Establish Efficacy

When there is strong evidence 1) to support similarity of disease between the reference and target population and 2) that exposures in the reference population will provide similar response

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

Endpoint: Target exposure metric

When the pediatric extrapolation strategy relies on matching adult exposures, the target exposure metric(s), range, and acceptance criteria should be prospectively specified and should be defined in the context of the disease, treatment regimen, route of administration, and formulation. The target exposure metric should be based on the exposure range associated with treatment response (efficacy and/or safety) and can be derived from established exposure-response relationships or observed data in the reference population. The selected target exposure metric(s) should be associated with the treatment response, and an adequate discussion and justification should be provided based on, but not limited to, the mechanism of action and the metrics previously established in the exposure-response relationships in the reference population. It is often useful to present several exposure metrics. For example, AUC0-t or Cmin may correlate with efficacy whereas Cmax may be more informative for safety. In cases where systemic exposure does not correlate with efficacy (e.g., most locally acting drugs), additional assessment of response might be needed (see section 4.1.3.2 and 4.3).

Sample size

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

- The availability of patients in a specific body weight/age range
- The adequacy of the sample size to demonstrate precision in key PK parameters in the pediatric population such as clearance and volume of distribution
- The adequacy of the sample size to match the pre-specified target exposure range (e.g., the interquartile range for the PK metric(s) in the reference population)
- The methodology(ies) used to determine the sample size

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

Analysis and reporting

Different presentations of the exposure data in the target and reference populations should be available to inform regulatory decision making. A single acceptance boundary for all drug products and drug classes (as compared to bioequivalence testing) will not provide a meaningful approach in the setting of pediatric extrapolation. An evaluation of confidence intervals for the mean differences in key exposure metrics such as AUC and Cmax could be an acceptable approach. The chosen boundaries of the confidence interval should reflect the context of the therapeutic range of the drug and the risk-benefit of the product for a given pediatric indication.

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

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

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

4.1.3.2. When Effect on a Biomarker is Needed to Establish Efficacy

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

- Use of a validated biomarker as a surrogate endpoint is recommended but not required.
- The choice of the biomarker endpoint should be supported by available data in the reference and target populations and justified in the extrapolation plan.
- A biomarker on the causal pathway that is correlated with clinical efficacy in the reference population is often acceptable and should be justified also with regard to its relevance to the target population.
- Models can be used to estimate the quantitative relationships between biomarkers and clinical efficacy (see section 3.6).

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

Sample size

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

Analysis and reporting

The data used in the analysis should be described, with a focus on the important elements relevant to the objectives of the analysis, i.e., the comparison between the biomarker effect in the target population and that in the reference population. A therapeutic range of the biomarker effect that provides a meaningful assessment of similarity between the reference and target populations should be pre-defined.

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

4.1.4. Other Considerations

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

4.2. Model-Informed Approaches

Modeling and simulation approaches are powerful tools that can be used, for example, to examine and inform study design, derive dosing recommendations, or perform sensitivity analyses. Quantification of relevant relationships (e.g., dose-exposure, exposure-response) provides an important foundation to conduct simulations in support of the dose selection. In addition, simulations of therapeutic window(s) associated with relevant PK or PK/PD endpoints can be explored prior to conducting a pediatric study. Modeling and simulation can be used to validate the pediatric extrapolation concept after completion of the pediatric study. When simulations are used for regulatory decisions, it is important to provide information that the models are fit for simulation purposes and that model assumptions and the simulation set up are clearly reported. Typically, this information would be provided in the form of a modeling and simulation plan that the sponsor generates for internal documentation purposes but is also suitable for interaction with regulators.

The availability of the various data sources dictates, in part, the methodologic approach, with

more top-down approaches (e.g., traditional PK/PD, population-based PK/PD) reliant on adult data and bottom-up approaches (e.g., PBPK, QSP) dependent on physicochemical, in vitro and preclinical in vivo data. For ADME prediction, data of interest include the physicochemical properties of the drug, in vitro data describing individual PK attributes, PK/PD data from preclinical in vivo experiments, and any PK/PD data from adults.

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

When making model-based assessments, the components of the model may have complex interrelationships (e.g., correlation of parameters and/or assumptions) that should be captured in the structure of the model along with any time dependencies. These features should be incorporated into the model at inception. Model equations and assumptions underlying the model structure or dataset should be clearly presented so that their relevance to the overall strategy, model predictions and elements of uncertainty can be properly assessed. Not all data and model elements are equally valuable; therefore, assumption testing is an important aspect of any extrapolation exercise and should be integrated into the analysis plan and report. Given the scope of model assumptions, there should be multidisciplinary input to fully evaluate the assumption-testing exercise.

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

4.3. Efficacy Studies

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

4.3.1. Single Arm Efficacy Studies

In some situations, single arm studies may be the most appropriate way of generating the required evidence. This would be the case, for example, when the standard of evidence in the

reference population is a single arm trial. When designing the study, how the primary efficacy objective would be evaluated should be defined using a pre-specified threshold.

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

4.3.2. Externally Controlled Studies

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

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

4.3.3. Concurrent Controlled Efficacy Studies

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

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

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

4.3.4. Incorporation of External Data

When identifying which information will be incorporated into the analysis of the pediatric study, relevant data should be identified through a systematic search using pre-specified selection criteria. Ideally, the sources of information to be leveraged should be agreed upon with regulatory authorities ahead of time. However, it is possible that the external data themselves may not be available yet, for example, if generated from trials running in the reference population in parallel to the study in the target population or borrowed across age groups in the same study.

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

4.3.5. Quantifying the Impact of Use of Reference Data

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

If Bayesian approaches are used, different ways of using the prior information, for example, by using a mixture prior or power prior, will have a different effective sample size depending on the choice of parameters used in the model. If such strategies are employed, sensitivity analyses looking at the effective sample size under different values of these parameters will better help understand the design properties. Regardless of the approach used, the method of borrowing proposed should be pre-specified, and sensitivity analyses to understand the effect on operating characteristics of different amounts of borrowing will better help understand the design properties.

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

It can be possible to base a pediatric extrapolation plan using a biomarker, surrogate endpoint, or

clinical endpoint as the primary endpoint in the target population, even if it is not the primary endpoint in the reference population [see ICH E11(R1) section 5.1.1]. In this scenario, an evaluation of the robustness of the correlation of the proposed endpoint to the primary efficacy endpoint in the reference population should be conducted. Where relevant, it may be prudent to initiate the evaluation of potential pediatric endpoints as part of the adult development program prior to their incorporation into the pediatric program.

4.3.6. Presentation and Justification for the Pediatric Trial

Diagrams that represent the overall planned trial design for the extrapolation plan are helpful, especially if the design is complex. This may be the case if, for example, there is an adaptive design, or a trial with multiple stages evaluating different aspects of clinical development in each stage. When evaluating a trial design, determining what potential results will lead to a successful study based on pre-defined criteria can help to understand what magnitude of treatment effect would need to be observed for a trial to be declared a success. Tables or plots of different critical thresholds could be useful if there is uncertainty around the most appropriate threshold.

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

4.3.7. Analysis, Reporting, and Interpretation

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

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

Ideally, the interpretation of a study is aided if the success criteria are described and agreed upon in advance with regulatory agencies. The criteria for success can be a p-value, or if reference data are explicitly borrowed, Bayesian success criteria, such as credible intervals, excluding critical values, or the probability that one treatment is better than the other by at least a certain pre-specified amount. More than one success criterion may be appropriate. For example, if a non-inferiority margin wider than would be accepted in adults is used, it is also possible to specify the point estimate of treatment effect that would need to be demonstrated for non-inferiority to be met for any given sample size and variance. This could help in demonstrating

efficacy by providing additional reassurance of the expected treatment effect. It is important to understand how similar the target data are to the reference data and to use metrics to define such similarity. If the observed data in the study are not similar to the observed reference data, this may limit the applicability of the pediatric extrapolation concept and the amount of data that may be considered reasonable to borrow.

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

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

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

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

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

5. Additional pediatric extrapolation plan considerations

5.1. Safety Plan

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

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

5.2. Inclusion of Adolescents in Adult Trials

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

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

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

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

trial.