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# Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Final

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# Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Final

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# Executive summary

For the purpose of this Reflection Paper extrapolation is defined as 'extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), or in related conditions or with related medicinal products, in order to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the amount of, or general need for, additional evidence generation (types of studies, design modifications, number of patients required) needed to reach conclusions'.

A marketing authorisation (MA) is granted based on provision of adequate evidence on clinical efficacy and safety. Depending on the therapeutic area and pharmacological parameters of a compound, evidence of efficacy might comprise demonstration of short-term effects, maintenance of effect and / or effects on long term clinical outcomes. These, and the respective objectives in respect of safety, are reflected as multiple specific research questions to be addressed in a clinical development programme.

The main focus of this document is to provide a framework for extrapolation as an approach to generate evidence on one or more specific research questions to support regulatory assessment of MA application in a target population. Specifically, the document promotes the use of quantitative methods to help assess the relevance of existing information in one or more source populations to one or more target population(s) in respect of the disease, the drug pharmacology and clinical response to treatment.

Based on this, expectations on the effects of treatment in the target population can be formulated. These expectations will be based on knowledge of effects in the source population or populations, and knowledge or assumptions about factors related to the target population that might modify those effects. Tests and trials can be undertaken to address gaps in knowledge and assumptions, so that the totality of available evidence can address the specific research question of interest in the target population. The principal elements of the framework are:

**Extrapolation Concept:** Existing information about the disease, the drug pharmacology and the clinical response to treatment should be collated across the source and target populations. Factors that might modify the effects of treatment between source and target populations should be identified. This might include the phenotype or severity of disease, maturation factors influencing exposure or the presence of the drug target, and the symptoms or outcomes important for establishing patient benefit. The primary focus will usually be to establish a line of reasoning about the relation between dose, exposure, pharmacodynamic (PD) effects and clinical responses. Where data are available to establish that a relationship (e.g. exposure-response) in the source population will apply equally in the target population or that a particular factor has little or no influence on the effects of treatment this knowledge can be incorporated into the extrapolation concept and will not need to be addressed in the extrapolation plan. For other relationships or factors, reliable and informative data might not be available. These gaps in knowledge give rise to assumptions in the extrapolation concept that need to be investigated in the extrapolation plan before the expectations on the effects of treatment in the target population can be considered as a sound basis for regulatory decision making.

Where possible, quantitative methods should be used for the collation of available data and the investigation of potential modifiers of the treatment effect. A structured documentation should be provided.

**Extrapolation Plan:** The gaps in knowledge and the assumptions identified in the extrapolation concept determine the objectives(s) and methodological approaches for the tests and trials that need to be conducted to draw inferences that are relevant for the target population. These tests and trials should be conducted to generate evidence that strengthens and ultimately, based on success criteria,

confirms the extrapolation concept. Specifically, the extrapolation plan will address whether regulatory decisions can rely on the initial, or revised, expectations on the effects of treatment in the target population, or if more data need to be generated.

Extrapolation plans will differ according to the extent of assumptions in the extrapolation concept. Data in the source population might establish that there are so few important modifiers of the treatment effect that clinical outcome can be predicted through similarity in drug exposure or in the magnitude of PD response. Alternatively, data from the source population might be limited such that the influence of one or more factors needs to be investigated through generation of some clinical data in the target population. The extreme case would be where gaps in knowledge might be such that extrapolation is not a viable approach.

**Mitigation of uncertainty**: Whilst conclusions from an extrapolation approach can give a sound basis for regulatory decision making, the data generated may not be sufficient to address all uncertainties related to a specific research question in the target population. For example, an acceptable degree of patient benefit on short-term efficacy outcomes, sufficient to support authorisation, might be established based on an extrapolation approach, but quantification of how this effect translates into longer-term outcomes might not be available. Alternatively, extrapolation based on similar exposure between source and target populations might be a sound basis for decision making, but the quantification of clinical benefit might benefit from being made more precisely. When there is a well-reasoned scientific uncertainty to be addressed to enhance the understanding of the effect of treatment with implications for better labelling and better use in clinical practice, the extrapolation plan can continue post-authorisation in order to reduce the identified uncertainty.

An exhaustive list of methodological approaches is not provided. The framework should encourage exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify their choice. While the focus is on extrapolation for the development of medicines in children, the underlying principles may be extended to other areas.

# 1. Introduction

The Paediatric Regulation came into force in the European Union (EU) on 26 January 2007. The Regulation aims to ensure that medicines for use in children are of high quality, are ethically researched and are authorised appropriately. Children should have the same opportunity as adults to use safe and effective drug products.

In general, development of medicinal products proceeds with non-clinical and clinical studies designed prospectively based on evidence that is accumulated in respect of mechanism of action, pharmacokinetics (PK), PD or clinical efficacy. Evidence generated in one or more source populations may be sufficiently relevant to another target population that it can support subsequent development in that target population.

In consequence, the evidence needed to address the research questions that are important for marketing authorisation of a given product in the target population might be modified based on what is known for other populations (see section 5.1). The requirements for evidence generation to support licensing in the target population will be a continuum, ranging from identification of an appropriate posology for the target population (only based on PK characterisation where there is evidence to support that achieving a similar exposure in the target population is sufficient to expect similar efficacy, see section 5.2.1.1) through to a full clinical development in the event that no extrapolation is possible (see section 5.2.1.2). It is appropriate to take advantage of existing information when planning and evaluating clinical studies in children. A more targeted generation of evidence should help to ensure that children only participate in clinical trials with specific objectives that further the scientific understanding of a medicinal product for use in children and, address the requirements for regulatory decision-making.

# 2. Scope

This reflection paper aims to provide guidance to applicants and assessors on the main regulatory requirements that are expected to be met for the use and the evaluation of extrapolation approaches in the development of medicines for children. The focus of the paper is on the use of extrapolation to address one or more specific research questions, related to either efficacy or safety, that are part of a broader paediatric development plan aimed at MA. The paper aims to promote the use of available evidence and objective criteria to support extrapolation. The principles outlined should encourage further exploration of potentially suitable methods for specific situations, and choice of strategies should be justified. The choice of quantitative methods to use in each step of the extrapolation exercise and methodological issues related to their application are appropriate topics for discussion through Scientific Advice.

While the focus is on extrapolation for paediatric medicines development, the underlying principles may be extended to other areas.

# 3. Legal basis and relevant guidelines

This reflection paper should be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83/EC as amended, all other pertinent elements outlined in current and future EU and ICH guidelines and regulations especially those on:

- ICH E11 and ICH E11 (R) 1: Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)

- Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (EMA/CHMP/458101/2016)
- Guideline on the role of Pharmacokinetics in the development of medicinal products in the Paediatric Population (CHMP/EWP/147013/2004)
- Guideline on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06)
- ICH Topic E 4 Dose Response Information to Support Drug Registration ( CPMP/ICH/378/95)
- Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005)
- Guideline on the investigation of medicinal product in the term and preterm neonate (EMEA/267484/2007)
- Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005)
- Scientific guidance on post-authorisation efficacy studies (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015)
- CHMP Therapeutic areas guidelines
- Guideline on clinical evaluation of new vaccines (EMEA/CHMP/VWP/164653/2005)
- Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations IV: Paediatric population, EMA/572054/2016
- Qualification of novel methodologies for drug development: guidance to applicants (EMEA/CHMP/SAWP/72894/2008).

# 4. General considerations

Extrapolation is based on information in one or more source populations (e.g. adults and/or children) being relevant to the target population (e.g. other paediatric population), in a way that can be quantified and used as a basis for further development. For example, in situations where the PK is established to be predictive of the clinical response, the influence of factors that determine exposure, such as body size and organ maturation can be investigated. Quantifiable links between population characteristics (body size, age and maturation), drug exposure (PK), pharmacodynamic response (PD) and clinical efficacy become, in this example, the foundation for the extrapolation concept (see further below).

To obtain a marketing authorisation it is necessary to establish therapeutic efficacy and a positive benefit-risk. Research questions are developed, usually to be addressed through the objectives of a clinical trial, or series of clinical trials. For example, it might be necessary to investigate dose-ranging, demonstrate onset of therapeutic efficacy, maintenance of effect and to quantify the safety profile. Having identified research questions of interest for a development targeting a marketing authorisation, one or more **extrapolation concept(s)** can be developed through synthesis of available information including characterisation of differences, specifically potential effect modifiers, between source and target populations. Extrapolation concepts are limited to those research questions of interest that can be addressed on the basis of extrapolation, i.e. where relevant and reliable data in a source population already exist. Other research questions of interest, where information from the source population is of no, or negligible, relevance or is not of appropriate quality, still need to be addressed elsewhere in the development plan but can be handled outside of the extrapolation concept and plan. The extrapolation concept will identify the existing evidence and the gaps in knowledge that need to be filled in order for

expectations on the effects of treatment in the target population to be formulated. For example, if the relationship between a particular PK metric or PD response and efficacy is well quantified and is applicable to the target population, it may only remain to determine the dose that gives similar PK or PD response.

Important gaps in knowledge and assumptions should be addressed based on specific study objectives and designs that are documented in the **extrapolation plan**. If the objectives of these studies are met the extrapolation concept might be considered valid. Otherwise the extrapolation concept and plan should be revisited. **Mitigation of uncertainty** for residual uncertainties may continue to be addressed post-authorisation. It is important to seek regulatory agreement on an extrapolation concept and proposed extrapolation plan before studies are conducted, and again for important changes to the concept or plan as data in the target population emerge.

Chronologic age alone may not always be the most appropriate categorical determinant to define developmental subgroups in paediatric studies. Physiological development and maturity of organs, pathophysiology and natural history of the disease or condition, and the pharmacology of the investigational product are factors to be considered in determining appropriate paediatric subsets, and hence the source and target populations for extrapolation. Accordingly, it may be justifiable to include paediatric subpopulations in adult studies or adult subpopulations in paediatric studies. When there is sufficient understanding of the pathophysiology and the pharmacology of the investigational product to support extrapolation across a range of age subsets, studies might particularly focus on those age subsets or disease subsets where gaps in knowledge are greatest (e.g. infants and neonates). Confirmation of an extrapolation concept to these more extreme age or disease subsets might justifiably support interpolation to e.g. intermediate paediatric age subsets.

The clinical studies in the source population that are intended to inform the extrapolation concept (in adults and/or in children) will need to be designed accordingly. It might be necessary to introduce specific clinical study design elements in trials of the adult population (e.g. additional timepoints, dose-levels, biomarker, a wider distribution of body weight) to inform and strengthen a future extrapolation concept for development in paediatrics.

If any aspects related to disease, drug pharmacology and/or clinical response between the source and the target population can be quantified with sufficient precision, an extrapolation concept might be constructed based on the relationship between dose, exposure and pharmacodynamic response or efficacy. Equally the understanding of disease and pharmacology might be such that a mechanistic model can be developed. Where gaps in understanding of disease or pharmacology are greater, the use of existing knowledge from source population and clinical data in the source population might still be relevant to inform and optimise the development required in the paediatric population (Section 5.2.1.2) The development programme in a target population will be driven not only by the content of an extrapolation plan but also by rational drug development (e.g. study of lower dose levels to confirm safety might be ethically mandated in circumstances where the potential incidence, or degree of toxicity is of particular concern before administering a dose that is expected to be efficacious). Evidence for efficacy and benefit-risk generated within the framework of extrapolation should result in the same quality of regulatory decision-making as that based on self-standing clinical trials. Assessments of efficacy and benefit-risk are often associated with uncertainties and this will also be the case when the clinical data generated in the target population are to support extrapolation. Where uncertainties underlying extrapolation are not fully resolved by the time of marketing authorisation, despite evidence to support a conclusion of efficacy and a positive benefit-risk ratio, these might be addressed through additional follow-up clinical data generated post-authorisation.

Applicants are encouraged to discuss extrapolation prospectively with regulatory authorities early in the drug development process. This includes discussion of study design in a source population to allow

extrapolation (e.g. collection of biomarkers), the appropriateness of data sources (e.g clinical trials, electronic healthcare data, registries) and quantitative methods used identify gaps in knowledge and to construct an extrapolation concept, the content of an extrapolation plan including study objectives and the use of endpoints in the target population other than those describing clinical efficacy, the use of pharmacometric and statistical models, and the identification of suitable study designs and data sources. In keeping with the concept of life-cycle, there may be circumstances where there will be the need for intermediate steps to confirm key assumptions before initiating the studies in children that will confirm the extrapolation concept.

# 5. Proposed Framework:

## *5.1. Extrapolation concept: synthesising evidence to identify gaps in knowledge and to derive expectations for effects in the target population*

Evidence generated in adult and paediatric populations with relevant diseases or conditions should be used to develop the extrapolation concept. Non-clinical evidence can also be important in understanding drug pharmacology. Ultimately the exercise should identify if there is already sufficient evidence to support paediatric extrapolation, i.e. if effects can be reliably predicted in the target population, or if additional clinical information is needed. For therapeutic areas and specific mode of actions where extrapolation is accepted in relevant CHMP guidelines, with validated endpoints and/ or qualified models, an extensive extrapolation concept wouldn't be required to justify the rational for extrapolation. Nonetheless, these scenarios should be planned and agreed prospectively with regulatory authorities at an early stage.

This section highlights how to build the extrapolation concept.

### 5.1.1. Existing knowledge and data sources to develop the extrapolation concept

All relevant data should be thoroughly reviewed to identify potential differences between characteristics of the source and target populations e.g. body size (body mass index (BMI) or body surface), age and maturation, pre-treatment condition (e.g. immune status for vaccines) and their relationships to drug exposure (PK), pharmacodynamic response (PD) and clinical efficacy or safety. Existing evidence to be integrated includes, when available, non-clinical data, disease pathophysiology, and consideration of the developmental physiology, and clinical data from the source and target populations. The data sources can be results from existing clinical trials, modelling and simulation reports and analysis, published literature, observational studies from healthcare databases or registries, expert panels and consensus documents.

It is inevitable that there will be uncertainty coming from the quality, completeness and relevance of data from the source population. Uncertainties could arise, for example, due to lack of consistency, coherence, and volume of evidence, complexity of exposure-response relationships or high biological variability and measurement error. Uncertainties that cannot be addressed through available evidence translate into gaps in knowledge to be addressed in the extrapolation plan through additional studies in the source or in the target population.

The strength of existing knowledge and the weight that can be attributed to it requires a combination of actual data and value judgements. In particular where qualitative evidence from expert judgement or consensus documents is used, (semi) quantitative methods that summarise value judgements can facilitate their integration with data and can facilitate discussion between sponsor and regulator.

Methodological issues of particular significance arise when using data from sources other than clinical trials conducted according to Good Clinical Practice, or when integrating evidence from different data sources. Examples include use of electronic health records, or data from treatment or disease registries, or where data generated in one of these data sources is to be combined with data generated in clinical trials, that might have been collected to different standards or with different methodology (heterogeneity in the methods in addition to variability between studies).

The evidence gathered at the stage of the extrapolation concept should provide a thorough understanding of both existing evidence that can substantiate expectations on the effects of treatment in the target population and the differences between source and target populations giving rise to factors that might modify the treatment effects observed in the source population.

### 5.1.2. Evidence synthesis leading to expectations for drug effects in the target population

Evidence synthesis should be conducted to derive expectations for drug effects in the target population. Structured documentation should be provided, detailing gaps in knowledge (assumptions) and including an assessment of the impact of identified uncertainties in the available source data and its synthesis (see 5.1.1). The potential similarities and potential differences between source and target population should be assessed using mechanistic and / or empirical approaches.

Gaps in knowledge, assumptions and uncertainties are usually structured around clinical pharmacology (the compound and the patient), physiology and disease considerations, and clinical response to treatment. In every area, empirical, mechanistic, mathematical and statistical assumptions underpin the data and any quantitative model that is used for integration of data or for quantitative predictions. When possible, quantitative methods should be applied to establish a line of reasoning about the relation between dose, exposure, pharmacodynamic effect(s) and clinical response(s) ((see extrapolation framework table):

- **Pharmacology (drug disposition and effect) to characterise existing evidence on exposure and exposure-response**: to investigate or predict the drug exposure (PK), the relationship between PK and pharmacodynamic response (PD) and clinical efficacy, and the impact of potentially important covariates (e.g. body size, organ maturation, genotype) based on physiological and maturation related differences in ADME, mode of action, PD-effects and toxicity. Doses to achieve similar exposure, or similar PD effect and acceptable safety per relevant subgroups in the target population should be predicted. When possible modelling of relevant data (in-vitro, animal and clinical data) should be used for example empirical population PK/PD, physiologically based PK (PBPK) modelling, systems pharmacology or other mechanism-based approaches.
- **Disease manifestation and progression**: to characterise similarities and differences between source and target populations based on physiological and maturation differences in aetiology, pathophysiology, manifestation and progression. Differences in natural course of disease progression in each of the relevant subgroups in the target population should be described and when possible predicted through quantitative synthesis of natural course of disease data or disease models
- **Clinical response to treatment (efficacy and safety):** to quantify the similarities and degree of differences between populations in clinical response based on physiological and maturation related differences. Degree of differences in efficacy, safety and benefit-risk balance per relevant subgroups in the target population should be described and when possible predicted by means of

quantitative synthesis or meta-analysis of existing treatment data, or disease response models, PK-PD-response models or systems pharmacology approaches.

When mechanism-based models are used, they should be qualified for the intended use. Expectations for qualification of a model used to reduce or to replace prospective data generation will be higher than those for a qualification of a model used to inform the design of a clinical study in the target population.

When more empirical approaches are used, appropriate statistical methods can be applied for comparison and for quantification of uncertainty (precision of estimated effects) between groups (e.g. a Bayesian framework or model-based meta-analysis). In either case, uncertainties related to the quality or variability inherent within the source data should be reflected. Quantitative approaches to elicit expert judgement that then allow the available data to be integrated with this expert judgement could be considered as part of the extrapolation exercise although there is limited regulatory experience in the application of such approaches. Scenario analysis based on ranges of plausible values or relationships for each assumption or uncertainty can help to identify which aspects are critical for examination in the extrapolation plan, specifically those where interpretation is not robust to different scenarios examined.

Expectations presented as explicit predictions from quantitative models represent the preferred approach, but when reliable predictions from quantitative models are not available statements of expected effects in relation to the effects in the source population might suffice. For example, that expectation of a magnitude of effect on efficacy would be similar to that in the source population.

### 5.1.3. Factors that could limit extrapolation

This section describes a series of considerations that can aid in determining whether, and to what extent, extrapolation is appropriate.

Factors that may preclude or limit extrapolation include but are not limited to the following:

- The target population is not sufficiently well defined or characterised in terms of, e.g., justified age cut-off and other patient factors besides chronological age making it difficult to identify and discuss potential effect modifiers between the source and target populations.
- There is inadequate evidence that the existing knowledge from the source population(s) is relevant to the target population or subgroup(s) of the target population, specifically where there are extensive gaps in knowledge on the pathophysiology of disease and the disease course in the target population or subgroup(s) of the target population.
- Important clinical outcomes (and hence endpoints) differ between source and target populations, increasing the complexity to set expectations, make predictions or integrate available clinical data.
- Data in the source population are inadequate (in quantity or quality) or are outdated and may not properly reflect current trends in patient management to such extent that the existing data would likely be different than prospectively collected data.
- Maturation and growth factors related to disease pathogenesis, disease progression, and pathophysiological, histopathological, and pathobiological characteristics can affect paediatric patients.
- The data generated in the target population cannot address the main uncertainties and assumptions underlying the extrapolation concept by the time of marketing authorisation (see section 5.3).

- Safety information from a source population (e.g: other paediatric population for another disease or from other drugs with the same of mode of action) may be used to predict short-term risks related to the mode of action of the drug and related to dose. However, considering that long-term risks related to growth and maturation cannot be extrapolated from adults, generation of new safety data are needed in the target population to address unexpected (age-specific) risks, thus to rely only on extrapolation for understanding of safety will not usually be possible, certainly for treatments intended to be dosed chronically.

## *5.2. Extrapolation plan*

The role of the extrapolation plan is to document approaches to reduce assumptions and uncertainties to the point that expectations outlined in the extrapolation concept can be confirmed as a reliable basis for decision making. In accordance with the requirements to obtain a marketing authorisation, regulatory decision making will be made on the totality of evidence: that which is available and agreed to be relevant from the source population and that which is generated in the target population. The plan will delineate those assumptions and uncertainties that need to be explicitly addressed before marketing authorisation, and those which can be addressed post-approval.

The initial extrapolation plan should allow for refinement given emerging information (e.g. natural history or epidemiological data relevant to similarity or differences in disease, PK, PD and clinical response) during the development program. When justified, the initiation of paediatric studies can depend on data from an initial study or qualification measure, these preceding studies should be outlined as interim steps in the extrapolation plan. The extent to which data will need to be generated in the target population lies on a continuum and may differ between subgroups (e.g.: age, maturation, genotype) of the paediatric population. Each extrapolation concept and plan will be individual but some general scenarios can be outlined for illustration. For example, where it is known that a particular exposure will achieve therapeutic efficacy, critical gaps in knowledge might relate only to establishing adequate dosing in paediatric patients by matching exposure levels (see also section 5.2.1.2, PK/PD). Examples of this could be antibacterial agents. Alternatively, when matching exposures is not sufficient but there is confidence in the similarity of disease such that therapeutic efficacy can be inferred from obtaining a target PD response, approaches that characterise the PK/PD relationship in the target population could be appropriate in addition to the PK characterisation in the target population. In both scenarios, adequate studies will be needed to establish the dosing recommendations (see also PKPD studies in the extrapolation plan). Finally, when there is remaining uncertainty on the predictability of the PD marker(s) on the clinical response, there might still be a need to generate at least some efficacy (and safety) data in the target population. Appropriate methodology must be used to support the proposed reduction in the amount of clinical data that need to be generated (see also section 5.2.1.3).

This section highlights how to develop measures to be proposed in the extrapolation plan. The measures should be to the extent possible, detailed in their pre-planning and clearly documented. The extrapolation plan should encompass all studies that contribute to extrapolation, including those to be conducted as post-authorisation studies (see section 5.3).

### 5.2.1. Design of studies in the extrapolation plan

The objectives of studies would differ between a study that is designed to explore safety and dose finding in order to inform the design of subsequent efficacy and safety studies in the target population and a study that aims to demonstrate similar exposure or PK/PD relationship between the source and the target population. For the latter, it is particularly important to justify and pre-define criteria to

evaluate the success of the study. For example, the magnitude of differences in exposure to be excluded in order to conclude that exposure is similar in the source and target populations.

All studies in the extrapolation plan should conform to applicable legislation and recognised international methodological and ethical standards for research.

Sections 5.2.2.1 and 5.2.2.2 provide general recommendations on the design of paediatric studies when extrapolation strategies are considered.

#### *5.2.1.1. Pharmacokinetic studies and pharmacokinetic / pharmacodynamic studies in the extrapolation plan*

PK and PD data will almost always need to be generated as part of the extrapolation plan to confirm an exposure profile, investigate factors that might modify exposure- response or justify dosing for clinical studies. Replacement of PK or PK/PD studies with model predictions is only acceptable if PK or PK/PD can be predicted with great certainty based on well-understood physiology, ontogeny and compound properties. In this scenario, in addition to convincing model evaluation, the systems part of the model should be qualified for the intended purpose. Early scientific advice is recommended to discuss such cases. Gaps in knowledge of intrinsic factors related to organ maturation and ontogeny of enzymatic and transport functions or pharmacogenetics and also extrinsic factors (e.g. diet, geographic), particularly in the youngest age groups of the paediatric population are sources of uncertainties and can affect the reliability in the predictions.

As described above (see section 5.2.1), clinical PK or PK/PD investigations may serve different purposes within an extrapolation plan. Clinical PK/PD studies that can be required as elements of a plan include:

- Characterise dose-exposure response relationships in different paediatric age groups with the objective to select paediatric doses to be investigated in further clinical efficacy/safety studies
- Characterise dose-exposure response relationships in different paediatric age groups which will then be used as basis for extrapolation and to support a paediatric posology without the need for further investigation in paediatric efficacy/safety studiesDepending on the PK and/or PK/PD study objectives various designs, different metrics of interest and decision criteria can be considered.

**Design considerations:**

Every effort should be made to design and power the studies to meet their objectives. Reference is made to the “Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population” (CHMP/EWP/147013/2004) for general guidance on PK/PD investigations. Methods for study design optimization such as methods based on Fisher-Information-Matrix and clinical trial simulations should be used as appropriate. Measures to handle unanticipated differences in PK/PD should generally be factored into the study design. Interim analysis or real time PK/PD evaluation may also be used to adjust doses in paediatrics.

There is a wide spectrum of approaches and study designs that may be acceptable to explore or confirm an adequate dosing rationale or specific assumptions in the extrapolation concept. Usually the dose regimen tested in paediatrics is the one predicted to give similar exposure or response to adults. However, more dose levels/regimens may need to be tested in paediatrics if the exposure response relationship is not known or cannot be assumed to be the same as in adults.

**Endpoints and success criteria:**

The choice of exposure metric(s), the PK/PD or PD endpoints and criteria by which similarity between source and target populations is assessed must be justified. Criteria can be developed as part of the

extrapolation concept, by thorough dose finding in the source population and description of the exposure-response relationship. For studies that aim to confirm assumptions of the extrapolation concept, the success criteria will need to be pre-specified.

For example if based on the extrapolation concept the exposure-response relationship is established to be identical in adults and relevant paediatric subgroups, then the objective of the PK study should be to identify the dose in different age groups that match the PK exposures that were related with clinical efficacy in adults. Still the relevant exposure metrics of interest, e.g. AUC0-t, Cmax, and the acceptable equivalence margins should be pre-specified. Ideally the study may be powered to meet a pre-specified and justified equivalence margin.

Even in this simple scenario it may be impossible to get comprehensive evidence in all paediatric subsets. For example there may be not enough infants to confirm a dose that gives rise to equivalent exposure in this population. Knowledge on organ ontogeny and enzyme maturation effects on PK could be incorporated when deriving exposure metrics of interest to help reduce uncertainties in this particular subgroup. An additional objective of the PK study in this subgroup may be to collect data to inform on maturation and body size effects of PK. The metrics, design and the power of study should be adapted accordingly. In every case modelling and simulation approaches (e.g. population PK, PBPK) incorporating knowledge of growth and maturation effects on PK are recommended to strengthen conclusions drawn from often sparse observed PK data.

#### *5.2.1.2. Therapeutic studies in the extrapolation plan*

Where confirmation of the extrapolation concept is based on similarity in PK or PD there might still be, in addition to PK/PD studies, the need to generate efficacy data from clinical trials as part of the extrapolation plan (or for mitigation of uncertainty). The objective of the therapeutic study might be to confirm a magnitude of effect on efficacy outcomes that is consistent with the one that was expected in the extrapolation concept. For other extrapolation plans, the generation of efficacy data will be specified as the pivotal evidence, perhaps at a nominal significance level that is higher than the conventional 5% two-sided level to reflect the justified use of information from the source population. Trial objectives should be specified accordingly.

**Design considerations:**

The following design aspects should be considered carefully:

***Choice of control group***: randomised, controlled studies, double-blind where feasible, are preferable in order to provide an unbiased estimate of the treatment effect. Estimates of treatment effects relative to control might form a better basis for comparison between the source and the target population than absolute changes from baseline within two different patient populations.

If it is not necessary to perform a randomised trial, the study proposed will still need to have a pre-specified analytical approach and criteria for success. The use of historical controls, or the generation of concurrent controls through a registry or other data source may be possible in some instances. The formal incorporation of historical controls with concurrent control data is possible, but inherently introduces further uncertainties to such comparisons. The historical controls, their management and assessment of outcomes should match the prospective trial population and procedures as closely as possible.

***Sample size***: studies should be adequately powered based on clear objectives aligned to the extrapolation plan. If the required sample size is not feasible because of constraints such as rarity of disease, target population or ethical considerations this should be addressed separately and not by

artificially amending study objectives, criteria for success or information to support the sample size calculation (e.g. the anticipated variability).

Once a reduced sample size supported by extrapolation of data from a source population has been justified, this should be translated to the prospective study design through appropriate statistical approaches. Examples of approaches could be using a higher nominal significance level than the usual 5% two-sided, widening a non-inferiority margin or using Bayesian methods to explicitly borrow information (e.g. from adult trials, from control groups, from other paediatric clinical trials). The acceptability and appropriateness of each approach will depend on the knowledge generated in the context of the extrapolation exercise, both in terms of the adult data and any paediatric data. Quantitative justifications should be provided for the extent to which the evidence generated in the target population is reduced. Uncertainties in borrowing information from external data sources should be reflected in the extent to which reductions in sample size are proposed. Borrowing information to such an extent that data generated in the target population would not dominate cannot usually be supported. The amount of information that can be included in the prior of a Bayesian analysis will always be decided on a case-by-case basis and based on the robustness of the evidence generated to date. It is important to quantify how much information will come from the prior relative to the actual data generated. The Type I Error properties of any Bayesian method should be investigated.

If there are subgroups identified a priori for whom it is important to generate sufficient data based on the extrapolation concept, stratification of the randomisation may be important, and recruitment may need to specify a minimum number of patients to be recruited in each subgroup (for example subsets based on pubertal development stage) to address specific objectives.

***Endpoints***: The selection of appropriate endpoints is a critical aspect of trial design. Studies should include clinical outcome endpoints, intermediate endpoints, or surrogates that are ideally relevant to all subsets of the target population. If a common endpoint is not meaningful across important subsets, more than one study may be needed.

Where it is necessary to investigate clinical efficacy in the target population, endpoints chosen should be clinically relevant to the paediatric population and should be sufficiently sensitive. Sensitivity of the endpoint is especially important if recruitment to a study is limited by feasibility constraints. As continuous scales are often the most sensitive to detect true differences between expected and observed efficacy, they may be more suited to provide a meaningful confirmation of extrapolation than those based on responder rates alone.

It is recommended to identify relevant endpoints and outcome measures as early as possible allowing, if needed, the investigation of endpoints for use in children during the trials in adults. Where different outcome measures are used in the source and target populations, where endpoints are more complex to interpret (e.g. composite or PROs) or in slowly progressive conditions, it may be required to collect supplementary data to address such uncertainties post-marketing (see section 5.3).

### 5.2.2. Regulatory confirmation of the extrapolation concept

If the data generated from the studies specified in the extrapolation plan are able to address the gaps in knowledge and assumptions identified in the extrapolation concept, according to the agreed criteria for success, the use of extrapolation to support regulatory decision making can be considered confirmed.

If the data generated do not confirm the extrapolation concept, e.g. the success criteria for similarity in PK or, PK/PD relationships are not met, or expectations for treatment effects on efficacy in the target population cannot be confirmed, additional work is required. The extrapolation concept and plan

would need to be updated (see section 5.2) to reflect the data generated and the ability to extrapolate should be reconsidered.

## *5.3. Mitigation of uncertainty*

If gaps in knowledge and assumptions are addressed through the extrapolation plan establishing a positive risk-benefit, a marketing authorisation can be granted. Nevertheless, the data generated in the target population may not fully address all uncertainties and assumptions underlying the extrapolation concept by the time of marketing authorisation. A formal, structured plan to mitigate residual uncertainties in the post-authorisation setting should be proposed as part of the extrapolation plan and updated in response to the results of the studies conducted. Where long-term follow-up studies are required to address uncertainties, high level planning for such studies should already be considered early in the development. Further studies, or continuing follow-up of patients from ongoing studies, should be designed to address specific uncertainties related to the understanding of therapeutic efficacy and/or safety with implications for understanding the benefit-risk of a medicine and with implications for better use of the medicine in clinical practice.

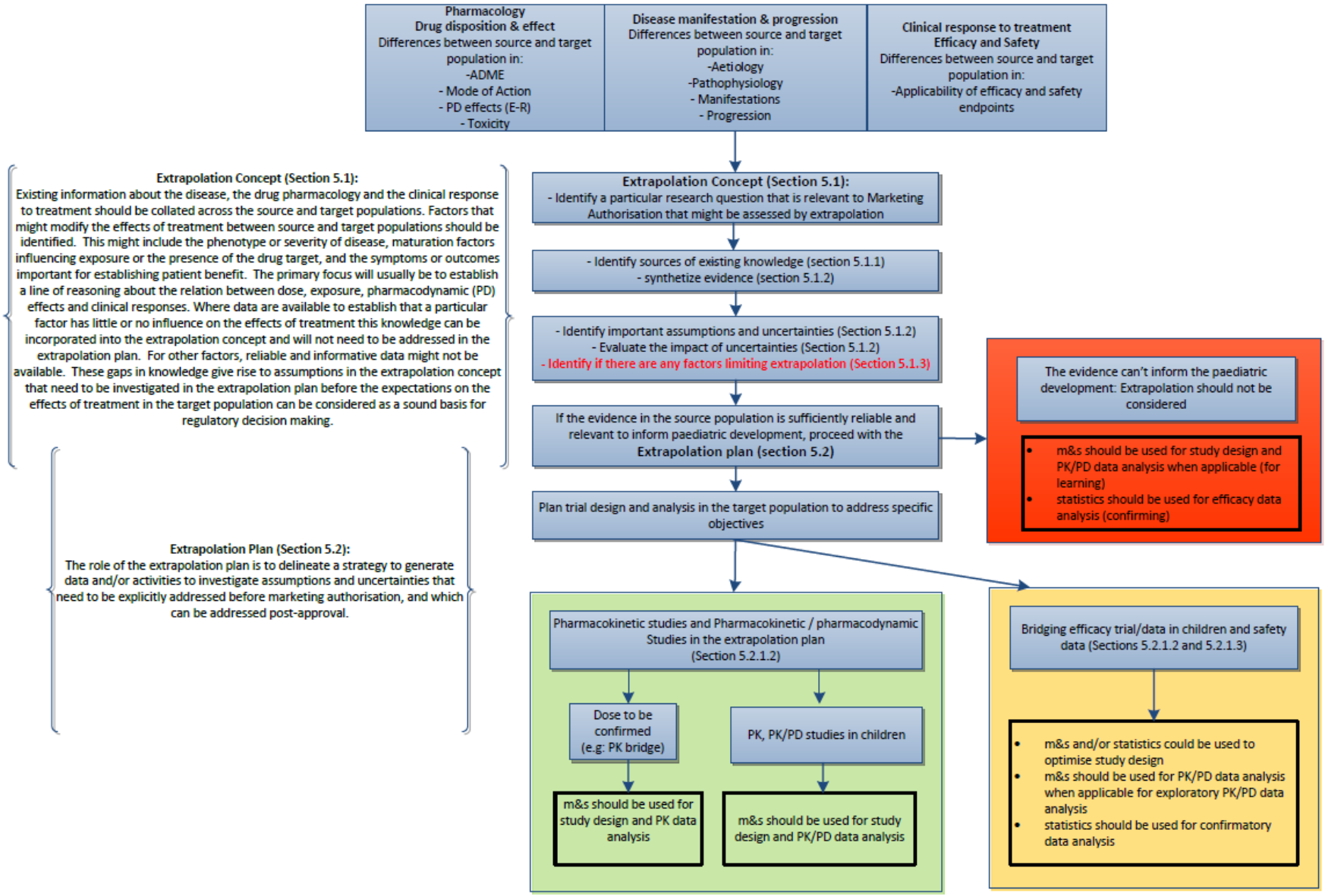
The quantitative tools used to build the extrapolation concept may also be used to quantify the uncertainties, their potential clinical implications and to inform useful mitigation measures, i.e. focused post-marketing studies.

Objectives should be addressed through designs that are ethical and feasible, taking account of the post-authorisation setting and which can be completed in a timely manner. Analytical approaches should give reliable and interpretable estimates of treatment effects. Often objectives of post-authorisation studies will relate to longer term effects of treatment. Long-term effects specific to the paediatric population may be defined as effects on the developing organs and organ-systems, e.g. on neurological, skeletal growth and sexual maturation (such effects may only become obvious, visible or identifiable in the long–term, i.e. with remarkable delay, in adolescence or adulthood). Therefore, adequate baseline assessments of growth/development and organ function, and regular follow-up measurements should already be considered early in the development to promote continuity between the data generation in the pre- and post-marketing phase. When post-authorisation studies are needed to fill potential gaps in the knowledge of the safety profile of the medicine, these studies should complement other activities such as signal detection performed on spontaneous reports.

If data sources other than clinical trials are planned, additional time for planning and regulatory dialogue might be required, in particular if it is necessary to start a new registry or amend an existing registry.

The requirements for Module IV of the Good Pharmacovigilance Practice, Paediatric population, the design and conduct of post-authorisation safety studies (PASS) in GVP Module VIII and the principles of the Scientific guidance on post-authorisation efficacy studies should be followed.

## 5.4. Decision Process for extrapolation



## *5.5. Examples of the Decision Process for extrapolation*

The examples in this section are intended to demonstrate the use of the decision process for extrapolation. The examples are not predictive of EMA decisions but may be considered guides for how EMA evaluate the appropriateness of extrapolation to support pediatric indications.

### 5.5.1. Where PK can be used as a basis of extrapolation

HIV infection is one example where it is assumed that the PK/PD -response relationship is independent of age.

Similar efficacy can be obtained from similar exposure in children to that observed based on efficacy and exposure data from controlled trials in adults. The CHMP guideline on clinical development of antivirals for HIV infection accepts extrapolation of efficacy from the adult to the paediatric population. Therefore in the extrapolation decision process it is established that there is no reason to expect a different response to the medicines in the different paediatric sub-groups. This is relevant to construct an extrapolation concept. The extrapolation plan could be based on a PK bridging approach with dose selection generally based on results from PK studies, where doses for different age groups are selected to produce plasma levels similar to those observed in adults. Safety would not be extrapolated. To mitigate uncertainties, assessments in the paediatric trials should be based on available non-clinical and adult clinical data while the need for long-term safety follow-up will be decided on a case-by-case basis depending on the uncertainties related to the pharmacology and target population under investigation.

### 5.5.2. Well-studied pharmacological classes

In the area of rheumatology, a better understanding of specific T cell subsets and associated cytokines has resulted in an introduction of novel biological products for the treatment of immune-mediated inflammatory diseases (IMIDs).

Pharmacological classes such as anti TNF alpha, can be considered pharmacological class about which a considerable amount of data has been collected in adults (e.g. licensed indication in one or more of the corresponding adult arthritis categories), or in children treated with the same medicinal product for other diseases, giving the possibility for an extrapolation concept to be formulated. Evidence might exist and be quantified to establish that there is no reason to expect a different response to the medicines in the different paediatric sub-groups. The extrapolation plan could be based on the existing knowledge, a formal efficacy trial may not be necessary. For example in juvenile idiopathic arthritis medicines where a clear PK-PD relationship and therapeutic window has been established in adult arthritis models, an extrapolation plan could be based primarily on PK and dose finding studies, supported with single-arm clinical data.

To mitigate uncertainties the results of the studies in the extrapolation plan, if agreed and used for marketing authorisation, may need to be supported by additional data reducing uncertainties on the magnitude of effect sizes observed in the target population.

### 5.5.3. Partial similarity in disease manifestations between populations

In the case of paediatric Gaucher disease, the impact of the different mechanisms of action and disease modifying factors (type of mutation, residual enzyme activity, age etc.) and epigenetic factors resulting in different presentations of the disease must be carefully considered. However, when it is

possible to identify specific characteristics of different patient populations, extrapolation can be considered.

Extrapolation of efficacy from adults to children may be considered for the somatic manifestations of both Type I and Type III Gaucher disease, such as visceral, hematologic and pulmonary disease, not neurological. The use of data from the adult Gaucher disease programmes should be maximised since this may reduce paediatric data requirements and it may support conclusions of efficacy and safety. Such knowledge could be used in predicting differences in PK, PK/PD, treatment-induced changes in different disease manifestations in the paediatric population giving the possibility for an extrapolation concept to be formulated. Hence an extrapolation plan could be formulated early during drug development, with the recognition that the plan may not address all research questions necessary in the development of emerging products across all ages of paediatric patients. Based on the existing knowledge, evidence that can establish a similar response to the medicines in the different paediatric sub-groups should be generated, such as effects of therapy on specific paediatric manifestations (e.g. growth rate, puberty and development). Additionally, studies should be planned to collect data to identify unexpected (age-specific) safety concerns not amenable to extrapolation.

It is also considered important to further inform on and learn about the causal genotype-phenotype relationships for disease traits that manifest differently between adults and children; the data collection should be planned from this perspective and opportunities for addition of informative endpoints should be considered. These aspects should be specifically addressed in paediatric studies.

The results of the studies in the extrapolation plan, if agreed and used for marketing authorisation, would likely need to be supported by post-marketing data (see section 5.3) reducing uncertainties on the magnitude of effect sizes observed in the target population across the spectrum of disease manifestations.

### 5.5.4. Examples where extrapolation is not recommended

In diseases where there are differences in terms of neurodevelopment stages, including growth, sexual and cognitive development that will impact on both efficacy and safety endpoints such as for the treatment of Autism Spectrum Disorder (ASD), constructing an extrapolation concept to make predictions for efficacy between paediatric age groups is difficult. Compensation strategies and management of the condition will vary between age groups and clinical data are needed to establish the age from which treatment is beneficial. Studies needed in adolescents and younger children should collect data to allow for assessment of consistency and interpretation in all age groups. Consequently, at present, there is no basis to consider extrapolation.

# 6. Submission and reporting of the extrapolation concept and plan

When developing an extrapolation concept and plan, it will be necessary to provide an overview of the existing available data and planned clinical data from the source and target populations. The basic principles of evidence-based medicine should be followed, especially with respect to a systematic approach, completeness of data, assessment and consideration of bias, and transparency of reporting. The available evidence, predominately data from the source population, should be the basis for the description of evidence synthesis and investigation of differences between source and target population. It should lead to a clear description of the extrapolation concept, and the associated gaps in knowledge (uncertainties) and assumptions.

When model-informed approaches are used, a modeling and simulation plan, including the approach to qualifying or evaluating a model for a specific purpose of use, should be submitted and discussed with regulators. All pertinent information regarding the model building and evaluation should be pre-specified as part of the extrapolation plan, including sources of data, study size and duration, relevant covariates, number of samples and sampling times. The relevant modelling and simulation reports should be submitted following the format proposed in relevant guidance documents.

A documented extrapolation concept and plan should be presented in regulatory procedures at e.g. Paediatric Committee (PDCO), the Scientific Advice Working Party (SAWP) or the Committee for Medicinal Product for Human Use (CHMP). Submission using extrapolation approaches as part of a paediatric investigation plan or a scientific advice should follow the procedural guidance available for the paediatric Committee or Scientific Advice Working Party respectively.

Once a test or trial that is part of the extrapolation plan has been completed, documentation of the extrapolation concept and plan should be updated, integrating the new information with existing knowledge and updating the extrapolation concept and plan, if appropriate. Details of the extrapolation concept and the results of the studies in the extrapolation will be included after marketing authorisation application in the European Public Assessment Report (EPAR).

# Extrapolation framework table

<table>
<tr><td rowspan="6">SOURCE POULATION<br>Adults and/or paediatric</td><td colspan="2"></td><td>Pharmacology<br>Drug disposition & effect</td><td>Disease manifestation<br>& progression</td><td>Clinical response to treatment<br>Efficacy & safety</td></tr>
<tr><td rowspan="5">Extrapolation concept</td><td>Mechanisms</td><td>Age/maturation-related differences in<br>- ADME<br>- mode of action<br>- PD effects (E-R)<br>- toxicity</td><td>Age/maturation-related differences in<br>- aetiology<br>- pathophysiology<br>- manifestation<br>- progression<br>- indicators</td><td>Age/maturation-related<br>- differences,<br>- applicability,<br>- validation<br>of efficacy & safety endpoints</td></tr>
<tr><td>Quantitative evidence</td><td>PB-PK/PD models,<br>Pop-PK/PD models<br>Quantitative systems pharmacology models<br>Covariates:<br>- body size, age, maturation, etc<br>- disease types, severity<br>- comorbidity</td><td>Quantitative synthesis of natural disease data<br>Disease progression models<br>Covariates:<br>- age, maturation, etc<br>- disease types, severity<br>- comorbidity</td><td>Quantitative synthesis or meta-analysis of treatment data<br>Disease response models<br>Covariates:<br>- age, maturation, etc<br>- disease types, severity<br>- comorbidity</td></tr>
<tr><td></td><td colspan="3">➢ existing data<br>➢ progressive input of emerging data</td></tr>
<tr><td>Inference</td><td>Predict doses to achieve<br>- similar exposure, or<br>- similar PD effect, and<br>- acceptable safety<br>by paediatric subgroup</td><td>Describe/predict differences in natural course of disease progression<br><br>by paediatric subgroup</td><td>Given similar drug exposure or PD response, predict degree of differences in<br>- efficacy<br>- safety<br>- benefit-risk balance<br>by paediatric subgroup</td></tr>
<tr><td colspan="3">➢ refine inferences using emerging data</td></tr>
<tr><td rowspan="4">TARGET POPULATION<br>Paediatrics, different paediatric subgroups</td><td colspan="2">Extrapolation plan and mitigation of uncertainties</td><td>PK studies or<br>PK/PD studies needed for confirmation of doses<br><br>in target population<br>Pre-clinical mechanistic studies</td><td>Epidemiological data<br>- natural disease course<br>- SOC treatment<br><br>in target population</td><td>- Design of clinical studies<br>- Sample size(s)<br>required in target population to conclude on benefit-risk balance</td></tr>
<tr><td colspan="2">confirmation of the Extrapolation Concept</td><td>Confirm<br>- modelling approaches<br>- identified assumptions<br>- confirm predicted differences in PK and PD<br><br>Establish appropriate doses in the target population</td><td>Confirm predicted differences in disease progression<br><br>Conclude on disease progression in target population</td><td>Confirm predicted differences in clinical response<br><br>Conclude on positive benefit-risk in target population</td></tr>
<tr><td></td><td colspan="3">➢ alternatively, adapt extrapolation concept and plan</td></tr>
<tr><td colspan="2">Further validation</td><td>PK/PD data from<br>- phase III trials<br>- post MA studies</td><td>Epidemiological data<br>Other drug developments</td><td>Post MA studies<br>Prospective meta-analyses<br>Pharmacoepidemiological data<br>Other drug developments</td></tr>
</table>