

22 January 2018

Submission of comments on *Reflection paper on the use of extrapolation in the development of medicines for paediatrics – EMA/199678/2016*

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA – Sandra Rodrigues (sandra.rodrigues@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* | |
| --- | --- | --- | --- |
|  | EFPIA welcome the publication of the Reflection Paper (RP) on paediatric extrapolation as a significant step forward in the use of extrapolation concepts within the development of medicines for paediatric patients. This should help minimising the burden on children and their parents from participation in clinical trials whenever relevant data can be generated via extrapolation.  However, to successfully implement the vision EMA has for sponsors to consider an extrapolation approach, EFPIA has the following important comments:    **Throughout the document, the meaning of extrapolation is not consistent:** it is first defined very broadly in the Executive summary (lines 33-38), but then it is stated for efficacy only in some sections, and then efficacy and safety in some other sections. Extrapolation can be applied in the areas of pharmacokinetics (PK), efficacy, and safety based on the broader definition on lines 33-38. Questions, assumptions, approaches and challenges for extrapolation and validation in each of these areas can be very different. Given the aim of this RP, it would be beneficial to clarify and provide points for consideration for each of these areas since the content in this current version of the RP seems only addressing extrapolation of efficacy.  **The RP should acknowledge that in some disease areas extrapolation is the most reasonable approach:** the introductory scoping of the draft reflection paper briefly refers to the ethical considerations associated with conducting clinical trials in children and adolescents. However, the approach does not fully embrace the spirit of the Paediatric Regulation (EC) No 1901/2006, which states that development of medicinal products for the paediatric population should be achieved without subjecting this population to unnecessary clinical studies. Hence, we would welcome further consideration regarding the circumstances where extrapolation approaches may reduce unnecessary study burden, both in relation to IMPs and especially placebo. Indeed, the current document seems to take an ‘all or nothing’ approach to extrapolation based on disease areas with HIV and infections specifically highlighted. However, there may be disease areas where a partial extrapolation approach may be warranted with appropriate risk mitigation activities in place to ensure that unnecessary exposure to children is minimised. The RP should acknowledge that in some disease areas extrapolation is the most reasonable approach, owing to ethical and feasibility constraints. An example of this could be SLE, which has been acknowledged by the rheumatology community (i.e. PRINTO), when suggesting open label PK studies. We are concerned though that the RP does not acknowledge that while extrapolation is an important an useful tool, sometimes even it cannot fill the gap.  **Extrapolation scenarios:** it is understandable that this RP cannot cover all possible scenarios. However, in discussing the extrapolation concept and later in the design section, it would be helpful to discuss those scenarios where there is not a similarity of disease or disease progression, but there is a common molecular target. It would be useful if the EMA could suggest that the data be used to assist in generating meaningful information for use in rare pediatric populations.  **Extrapolation in neonates**: The Agency’s specifically highlights neonates as a specifically challenging age group to extrapolate to. However, it is also in this age group where extrapolation may be of most value and where data generation, for a plethora of reasons, may be difficult to generate and ethical aspects are especially difficult. The current wording in the Reflection Paper suggests that extrapolation to this age group can only be based on clinical data generated in the same age group and that full extrapolation is not possible. In this regard, extrapolation may only be used to enhance study design and to inform dose selection.  It would be of great value to understand the Agency’s reflection on situations where full extrapolation can be used in lieu of conducting a clinical trial in a specific age group (e.g. extrapolating from toddlers to infants and neonates).  **Evidence generation:** the section on therapeutic studies seems to take it as a presumption that randomised trials will be needed in most cases and simply refers to the choice of a control group as being the main issue. There should be an additional section under 5.2.1.2 addressing non-randomised trials, acknowledging the role that non-randomised trials such as single arm trials, multi-cohort basket or umbrella trials could play in this setting.  In addition, is there a role for real world data either in terms of information generated under the rubric of RWD itself serving as extrapolation or indirectly using RWD to streamline and inform optimal design of therapeutic studies?  **PBPK** is considered an important aspect of extrapolation, and extremely useful for paediatrics. The reflection paper does not discuss this approach except for a brief mention in the Table on p.14. Suggest including it explicitly as one of the extrapolation approaches that might be useful for extrapolation of PK for different subgroups, with minimal need for confirmatory data.  **Quantitative methods:** The RP encourages the use of quantitative methods such as models and predictions, and conveys flexibility in the statistical approach, such as the use of Bayesian methods, and statistical testing at a significance level higher than the usual 5% two-sided. However, this does not appear to be the main content of the document, in which the extrapolation part is very general and top level and does not provide examples of relevant methods and how/when it is possible to extrapolate from a source to a target population. Instead the guidance concentrates on a detailed description of an “extrapolation plan” in which there are large sections that require detailed information on proposed PK/PD studies and therapeutic studies. It is not clear why this information should be repeated in a separate extrapolation plan when there is already a section in the PIP template that covers these aspects. We suggest that the focus of the guidance should be on relevant/acceptable methods that are appropriate for use in extrapolating data, especially in cases of rare diseases/ oncology when performing RCTs is not an option, and should provide relevant examples of cases where an extrapolation approach can be used instead of clinical studies.  **Interactions with regulators:** the agency should lay out the expected procedural pathway(s) for agreeing and modifying an Extrapolation Plan that meets the needs of both the PDCO and the CHMP including the PRAC. Please add guidance on how the new proposals in this RP would fit within the current PIP process and requirements. It would be more desirable to address the extrapolation considerations within the PIP. Otherwise, there can be significant duplication of information and complication in keeping consistency in different documents, and it could create significant work for both the sponsors and the agency reviewers.  Please update the PIP template to match the proposed extrapolation framework.  **An appendix with examples of acceptable approaches would be helpful:** the framework contains several concepts that should be developed in further detail for paediatric use, such as PKPD modelling, disease modelling and meta-analysis, and quantitatively driven study designs that collect PK and PD information. At present, there are only a few regulatory examples of successful application of some of the concepts laid out in the framework, including model-based or model-informed approaches. Developing such recommendations from a regulatory perspective, and in an evidence-based manner informed by either accumulated regulatory experience or exemplar cases that clearly motivate the need for “detailed” guidance, will provide an unambiguous policy framework for specific drug development issues.  Please consider providing more specific guidance and more detailed examples to illustrate concepts (e.g. combination of semi-quantitative and quantitative uncertainties) extrapolation plans.  **References to be added:** with the recent update in FDA’s paediatric Clin Pharm guidance, and ICH E11(R1), and the ongoing effort by ICH with E11A, it would be useful to harmonize the recommendations. Referring to articles such as Dunne et al, 2001, Sun et al, 2017 and the 2016 MID3 good practice white paper as “an” example of structured approach to documentation would help the readers to understand what is possible and not possible. Some contextualization within the regulatory environment: PIP and PSP would be useful.  **Consistency in using ‘children’ and ‘paediatrics’ would be useful:**  Switching between the words “children” and “paediatrics” becomes confusing, as children can be used to define a specific age group (subgroup) within the paediatric population as a whole (see ICH E11 for example categorisations). It is suggested using paediatrics throughout for consistency, then adolescents, children, infants, etc., can be used to describe specific subgroups.  **Terms and abbreviations are not defined:** it is recommended to include a glossary of terms and abbreviations.  In addition to these main comments, EFPIA has specific detailed comments on the text, which are included in section 2 of the document. |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | | Stakeholder number  *(To be completed by the Agency)* | | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- | --- | --- |
| **Executive summary** | | | | | |
| 37 | |  | | **Comment:**  “…, additional information…” Please consider replacing “information” with “evidence generation”  **Proposed change (if any):**  …general need for, additional ~~information~~ ***evidence generation*** (types of studies…. |  |
| 48-49 | |  | | **Comment:**  It is not always possible to quantify existing information about the disease, the drug pharmacology and the populations and therefore this statement should be qualified.  If the target is expressed in source and target population, the disease is existent in source and target and compounds with similar or even different MoA have been shown to be effective in source and target population, this would not need “quantification”.  **Proposed change (if any):**  “***Where possible*** existing information about the disease, the drug pharmacology and the populations should be quantified”. |  |
| 61-62 | |  | | **Comment:**  Suggest providing some caveats and further description around the word, “validates”. What constitutes “validation” with respect to extrapolation?  Instead of using ‘validates’ which can be confusing why not proposing ‘confirms’? |  |
| 67-68 | |  | | **Comment:**  In situations where additional data is gathered post-authorisation to address residual certainties it would be helpful to clarify if the general intent would be to include in the PIP or as a separate post-marketing commitment. If included in the PIP it may become very extended. |  |
| 69 | |  | | **Comment:**  “An exhaustive list of methodological approaches is not provided.”  The framework cannot provide an exhaustive list of methodological approaches, but at least some examples would be useful as guidance, especially for rare diseases where available data (also from source population) is limited. |  |
| 72 | |  | | **Comment:**  Please clarify what is meant by “… other areas.”?  Could this include other age subgroups (e.g., the elderly) and/or other aspects of medicines development (e.g., biosimilars development, devices)?  Please clarify and provide specify examples of other areas where these principles can be used. |  |
| **Introduction** | | | | | |
| 79, 84, 201, 206 | |  | | **Comment:**  “positive benefit-risk” is used in line 203 and in table on page 14, but in lines 79, 84, 201, 206 you write “positive risk-benefit”  Suggest using the same term eg “positive benefit-risk” throughout the document |  |
| 104-106 | |  | | **Comment:**  Further clarification is needed related to the statement that the “it would be unethical not to extrapolate since the understanding ….is so well established…”.  **Proposed change (if any):**  To facilitate more efficient medicines development for children, it would be helpful if the EMA could initiate and maintain a list (utilizing quantum of evidence) of scenarios where Extrapolation will be required in certain indications (or mechanisms of action based therapeutic development). |  |
| 109-110 | |  | | **Comment:**  “Eminence based” development can be inherently biased and introduce risk and therefore should also be quantified. Please clarify how the agency anticipates that sponsors should provide information from “… expert clinicians and expert pharmacologists …” as a basis to support extrapolation approaches. Is this intended to be through supportive documentation (e.g., literature), experts accompanying sponsors as part of Scientific Advice, other? |  |
| 117-119 | |  | | **Comment:**  What is the metrics for quantifying exposure-response that is considered favourable to carry out? F percentage coverage (50% vs 90%?) or statistical testing of similarity (p>0.05)?  Please clarify. |  |
| **Scope** | | | | | |
| 126-129 | |  | | **Comment:**  Additional information is required.  In order to align expectations and facilitate the selection and evaluation of the preferred quantitative methods, the document should provide, if not preferred methods, at least the minimum criteria for a quantitative method to be considered “adequate” by the Authority. |  |
| 130-132 | |  | | **Comment:**  “*Applicants are encouraged to discuss extrapolation prospectively with regulatory authorities, considering the potential for future extrapolation exercises even when designing studies to support initial MA in a source population*.”  Does that mean that all extrapolation concepts and plans should be a formal part of paediatric investigation plans? This would create additional work and might require several requests for modification once new data become available.  Or does it mean the extrapolation framework (concept and plan including risk mitigation) be presented as a stand-alone document supporting the PIP? While the PIP template contains a section for extrapolation, the document itself is limited in size and does not currently allow for inclusion of a detailed extrapolation concept and plan.  In addition, it may be helpful to modify as follows:  **Proposed change (if any):**  …to discuss extrapolation prospectively with regulatory authorities ***during the first PIP submission and further when first data in the target population are available***. |  |
| **General considerations** | | | | | |
| 155-157 | |  | | **Comment:**  In relation to proposing an initial paediatric extrapolation concept, is there preferred timing of PK in paediatric populations? Do you need to have adolescent or other age group PK earlier in the development plan to provide this quantifiable evidence for extrapolation based on PK? |  |
| 161-164 | |  | | **Comment:**  Clarification is required.  Does this mean that clinical trials that are needed to answer other questions of interest, should be excluded from the extrapolation concept and extrapolation plan?  Can you please provide clarification of the meaning of “handle outside the extrapolation concept and plan”? |  |
| 164-165 | |  | | **Comment:**  The extrapolation concept and extrapolation plan seems to be loosely referred to in the document. In other pages the extrapolation plan is to identify knowledge gaps but in many parts of the document, the extrapolation concept is referred to very similarly. We think the extrapolation concept is the synthesis of evidence necessary to support initial assumption of extrapolation. Conditional on this initial assumption, an extrapolation plan is made to identify the knowledge gaps.  Please clarify. |  |
| 168 | |  | | **Comment:**  "[PK and/or PK/PD relationship] ... is applicable to the target population ..." A more precise description of when a model is applicable would be very helpful in this context. E.g., which aspects need to be considered? Which conditions must be met and what defeats an application of these models? |  |
| 172-173 | |  | | **Comment:**  The so-called Extrapolation concept and Extrapolation plan are formal documents that need to be developed prospectively by the applicant and be approved by the Agency prior to initiation of the programme. It follows that any prospective data-driven modelling activity that is not included in the plan cannot be performed unless the plan is amended. Such a regulatory strategy amounts to a duplication of the PIP efforts and to a further leap in the administrative burden, a loss of agility and potential additional delays in the overall clinical development programme.  Also, in all circumstances, the agency consider that the applicant should bring forward the evidence supporting the extrapolation concept for any disease and target population, instead of the agency determining beforehand whether such extrapolation is generally endorsed. The burden of evidence gathering is thus transferred to all applicants individually and this is not an efficient process.  The agency may wish to suggest an overall strategy of extrapolation concept, extrapolation plan, mitigation plan etc, but should not impose mandatory review and approval at each step of the procedure which is of doubtful/questionable added value while tremendously increasing the delays and administrative costs. The obvious exception is when the extrapolation concepts are included in a PIP (which is to be approved and amended according to existing processes, which are already formal and time-consuming). |  |
| 174-176 | |  | | **Comment:**  “*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*.”  How exactly should such extrapolation concepts and plans should be handled? What are the procedural aspects to get agreement on extrapolation plans according to the proposal in the reflection paper? At the end of the reflection paper (line 468-471) it is stated that “Based on the extrapolation concept, the specification of key scientific questions of interest and specific trials listed with objectives, key design elements and criteria for success that can inform the size of the trial should be presented using the extrapolation framework in regulatory procedures at e.g. PDCO, SAWP or CHMP”, which provides some basic clarity about the interaction with authorities, although not in much detail. Scientific advice is not binding, so no formal agreement by SAWP, leaving only the PIP as a potential document for agreeing on extrapolation. |  |
| 176-177 | |  | | **Comment**:  The extent to which extrapolation may be applied differ not only by age groups, but may also differ by developmental stage (e,g. sexual maturation stages).  **Proposed change (if any):**  The extent to which extrapolation may be applied differ ***not only*** between age groups ~~of the paediatric population~~, ***but may also differ by developmental stage (e,g. sexual maturation stages)***. |  |
| 178-180 | |  | | **Comment:**  Usual approach is to start in older children and use the resulting data to extrapolate back to younger children. This statement suggests it could be appropriate to start in the youngest children first. Please clarify. |  |
| 180-181 | |  | | **Comment:**  It is unclear what “studies” the agency is referring to. Are these PK and or PKPD studies or clinical studies or something other?  Please clarify.  For purposes of efficiency and ensuring a more timely path to registration for children, it would appear counter-intuitive that an extrapolation approach would start with the age subset that has the greatest “gaps in knowledge”. It would seem a more prudent and ethical approach to start with the age cohort which most closely resembles or matches that of the source population and generate more information to build the set of information that then feeds back into the extrapolation approach to better inform where there are gaps in knowledge. Please address.  Alternatively, is the agency recommending that extrapolation can be accepted in certain age groups such as school age or adolescents (also where adolescents could be included in adult studies) without more detailed studies and more resources should be spent on younger groups, e.g., <2 years where drug pharmacology is more likely to differ? |  |
| 180-181 | |  | | **Comment:**  The term ‘Interpolation’ is not defined per se. Could that be elaborated?  In addition, interpolation to other paediatric age subsets might then be justified.  **Proposed change (if any):**  Interpolation to other paediatric age subsets might then be justified***, with particular attention to the maturation of organ and systems, considering that data from older subgroups may not be informative for the younger subgroups***. |  |
| 180-181 | |  | | **Comment:**  Interpolation between paediatric age groups should only be acceptable if the interpolated aspect (e.g. PK) is well understood in the subsets between the well-described subsets. For example, weight-normalised clearance for some compounds may be very low in newborns (compared to adults) due to immaturity of the kidney and metabolising enzymes but could at the same time be increased in young children due to a relatively high liver weight and liver blood flow. Interpolation from infants to adolescents would in this case cause an underprediction of clearance in young children which in turn may result in underdosing.  **Proposed change (if any):**  Interpolation to other paediatric age subsets might ~~then~~ be justified***, provided that it can be shown that the subset for which the interpolation is performed is well understood and that sufficient understanding/data exists to support the linear interpolation***. |  |
| 183 - 186 | |  | | **Comment:**  Additional information is required.  It is necessary to clarify the impact of this recommendation in the future development and evaluation of clinical trials in adults, especially the context/criteria where this recommendation will apply e.g. diseases where both adults and paediatric population are affected. |  |
| 184-185 | |  | | **Comment:**  In cases where adolescent populations differ mainly by body weight from adult populations, a wide distribution of body weight in adult studies provides a valuable basis for extrapolation and dose discussion.  **Proposed change (if any):**  It may be beneficial to introduce specific clinical study design elements in trials of the adult population (e.g. additional timepoints, dose-levels or biomarker, **a wider distribution of body weight**) to inform and strengthen a future extrapolation concept for development in children. |  |
| Lines 190-195 | |  | | **Comment:**  It outlines the use of prior information to facilitate the development of paediatrics even when there are gaps in understanding of disease or pharmacology.  **Proposed change (if any):**  Adding examples of what this might look like would aid the understanding. |  |
| 197-199 | |  | | **Comment:**  It is unethical to purposefully administer a sub-therapeutic dose to generate information in a paediatric population unless this is part of a well-designed dose range finding study for the paediatric cohort, or there is pre-existing information available that may inform on a range of dosing to assess exposure-response or conduct exposure-matching. When “purposefully” administering a sub-therapeutic dose, we would only be introducing risk to a paediatric subject and no prospect of benefit.  **Proposed change (if any):**  This sentence should either be deleted, or re-worded to reflect the scenarios where it would be acceptable to do so. |  |
| 199-200 | |  | | “*In some development programmes the studies required according to an extrapolation plan*”  **Comment:**  The sentence ends very abruptly, and obviously there is text missing. Please complete or delete. |  |
| 202 | |  | | **Comment:**  What is meant by “quality of regulatory decision making”?  Please clarify. |  |
| 203-206 | |  | | **Comment:**  It would be helpful to give examples of the follow-up data which could be generated (assuming it is different to the Follow up data for an adult MA).  Examples would also be helpful where the document discusses assumptions/uncertainties that can be addressed before the MA in the extrapolation plan and those that can be “addressed post-approval”.  The reflection paper refers to unresolved uncertainties in the extrapolation concept and additional follow-up data generated post-authorisation.    **Proposed change (if any):**  In order to provide clarity on what types of additional data may be required, examples of uncertainties in the extrapolation as well as follow-up data would be useful. |  |
| **Proposed Framework** | | | | | |
| Line 209  Section 5.1 | |  | | **Comment:**  This part would deserve a section on modelling: models are made based on assumptions, made to synthesize information and to quantify uncertainties, that is all about section 5.1. We would advise to articulate the extrapolation concept around model-based approach; other methods can be used for extrapolation but there is doubt they can synthesize information and quantify uncertainty. |  |
| 212-213 | |  | | **Comment:**  It would be beneficial to understand the Agency’s reflections on the utilisation of external data from another disease and/or drug with similar metabolic profile. External data may be further enriched by *in vitro* data pertaining to the target population. Which types of pre-clinical data would the agency consider relevant for supporting e.g. cross age range extrapolation? |  |
| 213 | |  | | **Comment:**  “Systematic review” typically refers to reviews according to evidence based medicine methodology, e.g. Cochrane Reviews. Suggest avoiding the word “systematic” in this context.  **Proposed change (if any):**  All relevant data should be ***thoroughly*** ~~systematically~~ reviewed to identify potential differences |  |
| 219-220 | |  | | “*(Semi) quantitative methods that summarise value judgements can facilitate their integration with actual data*.”  **Comment:**  Can the agency clearly elaborate or provide examples of semi-quantitative methods for value judgements? Is there a systematized method to quantify value judgements that the EMA endorses?  Examples (links to literature) exemplifying the use of these semi-quantitative methods should be provided to aid interpretation.  **Proposed change (if any):**  Add links to suitable references, indicating these are just examples, would aid understanding but also allow other approaches to be considered. |  |
| **Section 5.1.1** | | | | | |
|  | |  | | **Comment:**  The reflection paper (section 5.1.1) appears to be particularly focused on the use of quantitative methods for all parts of the extrapolation concept and extrapolation plan. However, the use of quantitative methods may not always be feasible, or required i.e. when similarity of disease (or disease progression) between adults and (subsets) of the paediatric have already been established.  It is suggested that these types of situations and the use of qualitative evidence be more explicitly described/addressed.  Also, it is not clear what quantitative data would need to be provided. The data to answer these questions, depending on disease area, and sponsor size and experience within that compound class is unlikely to be at hand for the sponsor to do quantitative informed decision, it is usually more qualitative experts’ opinions which is used. The RP should reflect what it is feasible to do and what it is being done, rather than the ideal. |  |
| 222 | |  | | **Comment:**  Before understanding the differences between target and source population, the variability (for example between study differences) within the target population need to be understood. This should be addressed from a clinical and from a data-driven perspective. For example, between-study differences which cannot be explained by known covariates. This establishes what differences must be considered as relevant or not and facilitates in defining margins to assess equivalence.  **Proposed change (if any):**  The similarities and potential differences between source and target population, ***and the variability (for example between study differences) within the target population*** should be assessed.. |  |
| 228-232 | |  | | **Comment:**  This seems very theoretical; an example would help to understand the “quantitative synthesis of natural course of disease data” or “quantitative synthesis of existing treatment data”? The question again is whether for assumptions around disease manifestation and progression and clinical response quantification is absolutely necessary  **Proposed change (if any):**  shift the third bullet (line 233-237) on top. Explain the conditional character of quantification for disease (manifestation and progression) and clinical response which may support assumptions on similarity of difference between source and target population |  |
| 230-232 | |  | | **Comment:**  Does this mean part of the synthesis could be based upon comparing response to other drugs? How similar would the drugs have to be? Please clarify. |  |
| 238-241 | |  | | **Comment:**  Adding reference to EMA impact assessment and /or link to EFPIA impact assessment (MID3 white paper) would aid understanding.  **Proposed change (if any):**  Consider adding links to impact categorisation (EMA or EFPIA sources or preferably both) and their use in facilitating transparency in communication. |  |
| 238-241 | |  | | **Comment:**  The Reflection Paper establishes the relevant guideline as ‘Guideline on the qualification and reporting of PBPK modelling and simulation’ however, it does not provide clarity on what EMA intends “qualification” to mean. This is important as we are assuming that what is implied within the text is qualification as a means to determine that a prediction is credible, and not as part of a more formal Qualification Procedure.  **Proposed change (if any):**  This could be addressed simply through the addition of a Glossary. |  |
| 245-247 | |  | | **Comment:**  Not sure what this means. Would an example of this be generating priors using a panel of experts for the use in Bayesian analysis?  What are EMA opinions when eliciting expert advices that would satisfy the extrapolation exercises?  Is it 1, 2, 3, or 10 expert opinions and how would this be documented and/or rigorously tested for example to support prior Bayesian testing?  Also, since it is also stated that there is limited regulatory experience in the application of such approaches, some references on literature/case studies on the application of this approach will be useful.  **Proposed change (if any):**  Provide further advice on how to gather and include elicited knowledge into the PIP process |  |
| 253-257 | |  | | **Comment:**  In this evidence synthesis and prediction section, safety information is introduced; however, safety information is critical in establishing a benefit-risk profile.  **Proposed change (if any):**  As safety is crucial to the benefit-risk evaluation, we recommend adding a statement in the Executive Summary highlighting the role of safety information and extrapolation. |  |
| **Section 5.1.2** | | | | | |
| 270-272 | |  | | **Comment:**  Regarding documentation of the assumptions it might be useful to point to the “assumption table” outlined in the publication on “Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation” (Marshall at al., CPT, Vol 5, p 93-122) as it nicely structures the categories mentioned here and provides a framework on how to document assessment and impact of assumptions |  |
| 273-282 | |  | | **Comment:**  The section addresses how uncertainties can be addressed using scenario analysis. Perhaps it’s helpful to indicate that uncertainties can also be addressed by Bayesian modelling.  **Proposed change (if any):**  ‘…addressed post-approval. ***Uncertainties can also be addressed within a Bayesian framework through informative priors.*** The scope of extrapolation (in particular…’ |  |
| **Section 5.2 Extrapolation Plan** | | | | | |
| 284-285 | |  | | **Comment:**  From the way the first line is written (‘An agreed extrapolation concept’), it is not clear that the role of the Extrapolation Plan is to delineate a strategy to generate data and/or activities to fill the gap and to investigate assumptions. If this is the role of the Extrapolation plan, maybe it would be worth clarifying. |  |
| 295, 300 and 304 | |  | | **Comment:**  References to specific sections within the document would be easier to read and follow if the Section number was used.  **Proposed change (if any):**  Lines 295 and 300, "(see also ***Section 5.2.1.1,*** PKPD Studies in the extrapolation plan)”.  Line 304, "(see also ***Section 5.2.1.2,*** Therapeutic Studies in the extrapolation plan)”. |  |
| 296–304 | |  | | **Comment:**  The examples are very useful in helping illustrate what is intended. It is suggested that this approach is used in other sections (as outlined above and elsewhere where possible).  **Proposed change (if any):**  Consider where examples may add context and understanding |  |
| 303-304 | |  | | **Comment:**  To align expectations and facilitate the development and review process, the criteria for a methodology to be considered appropriate should be included. Please consider adding information. |  |
| 305 | |  | | **Comment:**  One of the struggles with early implementation of the Paediatric Regulation was that PIP applications were expected to be highly detailed which led to a high degree of modifications through a formal Request for Modification procedure. Given this past experience, and as it is our expectation that an Extrapolation Plan is to be agreed as part of a PIP, the agency should include what their minimum requirements for agreeing a plan (e.g., planned sample size re-estimation at [X] milestone versus a key binding element with a specific sample size). It is concerning that this Paper is asking for “… as detailed as possible …” plans, in particular as extrapolation is expected to be iterative and therefore will very likely change as new data is generated. To this end, there is a risk of having a too detailed of an Extrapolation Plan within the PIP. We should avoid a situation where we have to repeatedly seek Request for Modification every time new data becomes available to update the Extrapolation Plan. We welcome guidance from the EMA regarding how to minimize PIP RfMs – balancing the need to achieve agreement on an extrapolation approach and the resource necessary to return for modification agreement. |  |
| 308 | |  | | **Comment:**  “6 minute walking test” example is useful but greater context is required to indicate what this relates to.  **Proposed change (if any):**  Add more information with respect to the example e.g. in a manner utilised effectively in lines 296-304 |  |
| 310-311 | |  | | **Comment:**  Further clarification will be helpful for “providing that they (surrogate or intermediate clinical endpoints) have been validated and that they account for the physiologic developmental changes in the paediatric population…”  What does the Agency mean by “validated”? There are very few end-points that are validated specific to paediatric subgroups.  **Proposed change (if any):**  It would be helpful to provide guidance or reference on recommended method(s) to validate surrogate or intermediate clinical endpoints which account for the physiologic developmental changes. |  |
| 319 | |  | | **Comment:**  “…should take account of new data and be reviewed before initiation of subsequent paediatric studies.” is unclear. What regulatory process should be followed and which authority should address the review?  **Proposed change (if any):**  Request clarification as to by whom the new data need to be reviewed. Does this imply the Applicant, or also by PDCO? Presumably only the latter where there would be a change to the PIP binding elements. |  |
| 320-321 | |  | | **Comment:**  There seems to be an implication that there may be some agreement on post-authorisation studies before the MA is submitted.  **Proposed change (if any):**  Request examples of the nature of post-approvals commitments that could be considered while developing the extrapolation strategy. |  |
| **Section 5.2.1** | | | | | |
| 340-341 | |  | | **Comment:**  In some instances, PK (analogous reasoning for PKPD applies, even if less common) may be very well understood, e.g. because of existing data from a closely related compound or because of straightforward PK determined by well-described physiology and ontogeny (example: exclusive renal elimination may lead to excellent predictions of clearance for all paediatric age groups due to well-understood maturation of kidney function). Even if these cases may be rare, they represent an important opportunity to use modelling and simulation approaches to replace part of the clinical studies thus saving resources and avoiding the burden of unnecessary trials in the paediatric population.  **Proposed change (if any):**  Replacement of PK or PKPD studies with model predictions for dose selection purposes is ~~normally not acceptable, as there still are gaps in existing knowledge of paediatric PK and PKPD~~ ***only acceptable if PK or PKPD can be predicted with great certainty based on well-understood physiology, ontogeny and compound properties. Model qualification with suitable PK or PKPD sampling in consecutive studies is appropriate.*** |  |
| 351-352 | |  | | **Comment:**  Statistical power is mentioned in a few places. If the study is to inform rather than validate the extrapolation, should the powering be such that the study is "stand alone" or only sufficiently to update the mathematical model being used for the extrapolation as part of a larger dataset? |  |
| 364-368 | |  | | **Comment:**  Powering may not be feasible in the context of a (paediatric) PK study. Suggest deleting the sentence.  **Proposed change (if any):**  Still the relevant exposure metrics of interest, e.g. AUC0-t, Cmax, and the acceptable equivalence margins should be pre-specified. ~~Ideally the study should 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 age groups. |  |
| **Section 5.2.1.1** | | | | | |
| 378-379 | |  | | ” However, more dose level may need to be tested in children if the exposure-response relationship is not known or cannot be assumed to be the same as in adults”.  **Comment:**  Quite likely when starting the paediatric development for the first time in children, the exposure-response for a drug is not known, you may be able to assume itis the same as in adults based on other similar drugs, or because it is the best assumption you can make. It may well be unethical and unfeasible to expose children in a study to doses that a priori are anticipated to not maximize benefit, as it says the previous sentence usually the dose regimen tested in children is the one that is predicted to give similar exposure as in adults. This ethical and feasibility constraint should also be reflected in the paper.  **Proposed changed:**  ” However, more dose level***s*** may need to be tested in children if the exposure-response relationship is not known or cannot be assumed to be the same as in adults. ***In this case a limited exposure-response relationship may be studied, depending on disease area and feasibility constraints, as it may not be feasible to enrol children if they may be exposed to doses that a priori are not expected to maximize benefit based on what is known from the adult source.*** Measures to handle…” |  |
| 340-341 | |  | | **Comment:**  PK of monoclonal antibodies tends to be similar in adults and children. In this situation, modelling and simulation may be acceptable in determining starting doses.  **Proposed change:**  Replacement of PK studies with modelling and simulation may be appropriate in certain circumstances but in general PK studies should be required. Suggest modifying sentence since there may be situations other than paediatrics where there may NOT be gaps in PK/PD.  **Comment:**  Are there any examples of where PK or PKPD studies for dose selection purposes can be replaced?  In addition, would it be possible to define what these youngest age groups would be? Is it 1 month or 2 years etc.  **Proposed change (if any):**  Clarify when it may be acceptable to replace PK or PKPD studies with model predictions. |  |
| 341-344 | |  | | **Comment:**  Extrinsic factor that can affect the predictions should be considered.  **Proposed change (if any):**  For example, gaps in knowledge of intrinsic factors related to organ maturation, ontogeny of enzymatic and transport functions or pharmacogenetics and also to 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. |  |
| 342-344 & 369-370 | |  | | **Comment:**  In Lines 342-344 the Paper says that there are “… *gaps in knowledge related to organ maturation and ontogeny* …” yet in Lines 369-370 the paper notes that systems knowledge “… *could reduce uncertainties* …” in infants. Is the agency meaning here that generation of information that enhances our current understanding of systems knowledge is needed? If so, then the sentence in Line 369-370 should be re-written to better communicate this need. As currently written, it appears to reflect that we could use existing system knowledge. |  |
| 352-353 | |  | | **Comment:**  “Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population” is made reference to, but the full reference to the CHMP would make this clear which paper they are referring to.  It is also suggested to add a reference list.  **Proposed change (if any):**  "Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population ***(CHMP/EWP/147013/2004)***". |  |
| 354 | |  | | “*Methods for study design optimization such as FIM-based methods, clinical trial simulations and adaptive study design should be used as appropriate*.”  A list of abbreviations should be considered.  **Proposed change (if any)**:  Replace FIM with Fisher-Information-Matrix -based. |  |
| 356-361 | |  | | **Comment:**  What are EMA opinions of the minimal success criteria to support extrapolation exercises?  In other words what is the equivalence threshold metrics that sponsor should strive for? |  |
| 362-363 | |  | | **Comment:**  How likely is it that PK/PD is established to be identical before the PK study? Matching exposure and doses will be derived from the PK/PD study (studies).  **Proposed change (if any):**  ~~For example if based on the extrapolation concept the exposure-response relationship is established to be identical in adults and children,~~ ***T***he objective of the PK study should be to identify the dose in 363 different age groups that match the PK exposures that were related with clinical efficacy in adults. |  |
| 366-367 |  | | **Comment:**  *“Ideally the study should be powered to meet a pre-specified and justified equivalence margin.”*  The equivalence criteria can depend on the disease area and population of interest and can be discussed during the generation of extrapolation plan with the regulatory agencies.  Suggest modifying the sentence.  **Proposed change (if any):**  “Ideally the study should ~~be powered to meet a pre-specified and justified equivalence margin~~ ***have adequate sample size and age-distribution to justify the conclusions emerging from the study. The strength of the extrapolation framework will depend on the totality of data for the age subgroup or special population***”. | |  |
| 377-380 | |  | | “*Usually the dose regimen tested in children is the one predicted to give similar exposure or response to adults. However, more dose levels may need to be tested in children if the exposure response relationship is not known or cannot be assumed to be the same as in adults*.”  **Comment:**  For some indications (e.g. oncology), paediatric sample size is limited and therefore limitations in testing different dose levels are to be expected. Might also be unethical to expose children to ineffective doses. It is also generally not clear why a guidance on extrapolation contains requirements on choice of dose regimens for clinical trials.  PK/PD studies are not part of confirmatory efficacy trials. It is self-evident that all trials should be optimally designed.  Proposed change (if any): Delete: The PK/PD studies may be standalone studies or be conducted as part of a confirmatory efficacy trial. In either case, it should be ensured that they are optimally designed for their purpose.  **Proposed change (if any):**  Suggest deleting lines 374 – 384 and referring to relevant guidance documents on clinical studies. |  |
| **Section 5.2.1.2** | | | | | |
| 385 | |  | | **Comment:**  Why the term "therapeutic" and not "clinical"? |  |
| 385 (Section 5.2.1.2) | |  | | **Comment:**  In case of validation (lines 386-387), why is it good enough to exclude large difference? Indeed, if the goal is to validate an assumption of similarity (e.g., paediatric efficacy versus efficacy predicted from the source), the validation of the assumption will result in approving the paediatric dose. In this case, one would like to apply confirmatory standing to the situation of validation, e.g. narrow equivalence margin perhaps at a higher nominal level than 5% to reflect the justified assumption supporting similarity.  So one could argue that both validation (lines 386-387) and generation of pivotal evidence (lines 388-390) should be considered similarly with a confirmatory-like criterion (equivalence limit for the validation and significant difference for confirmatory) and, for both validation and pivotal evidence, a released nominal level to reflect the justified assumption supporting similarity. |  |
| Line 393-396 | |  | | *Sample size*  **Comment:**  How do we really determine sample size? What if the number which is determined by statistical approaches is not feasible from a practical point of view, or because the disease is too rare. What does one do in such cases if (a) extrapolation is not possible and (b) the sample size required for a pivotal trial is not feasible?  **Comment:**  Do you follow the same recommendations as FDA when it comes to sample size of a PK study (Wang et al, J Clin Pharmacol 2012)? If so it would be able to mention it here, and reference the article.  **Comment:**  On the feasibility of the required sample size, would it be possible to clarify where and how this should be addressed (at the moment it states that it should be addressed separately but not where)? |  |
| 397-401 | |  | | **Comment:**  Some guidance will be helpful on the upper limit of the higher nominal significance level, the widened non-inferiority margin or amount of information may be borrowed from the source population.  **Proposed change (if any):**  Either provide general guidance in the document or provide reference to related guidelines. |  |
| 400 | |  | | **Comment:**  Widening of non-inferiority margins might dilute interpretation of evidence with respect to clinical relevance and should be restricted only to cases where clinically justified. Moreover, Bayesian methods are only mentioned in the context of explicitly borrowing information. However, similar like using higher significance levels than 5%, the Bayesian framework allows quantifying the degree of evidence with which the study objective is met.  **Comment:**  Would joint modelling of pooled (adult and other paediatric trial) data be an acceptable approach as well?  **Proposed change (if any):**  Change text to “… widening a non-inferiority margin ***if clinically justified*** or using Bayesian method to ***quantify evidence with an appropriate chosen probability threshold for success and/or to*** explicitly borrow information…” |  |
| 401 | |  | | **Comment:**  The list in the brackets suggests 3 potential sources to borrow information: from adult trials, from control groups, from other paediatric clinical trials. It is unclear whether this is the intended meaning or whether it is intended to mean either from adult trials or from control groups from other paediatric trials, or just the existing prior knowledge of relevance.  **Proposed change (if any):**  …borrow information (***eg*** from adult trials, from control groups, from other paediatric clinical trials).’ |  |
| 404-405 | |  | | **Comment:**  Acceptable level of uncertainties needs to be quantitatively defined to avoid ambiguity of whether data borrowed to supplement the gap in target population can be justified. An example or two would help. |  |
| 406-408 | |  | | **Comment:**  Please specify what “*extent that data generated in the target population would not be informative*” means.   * How and where do you define the cut-off for being informative? * What happens in case strong priors need to be defined for specific parameters, e.g. absorption rate? * Or is it a case by case decision depending on which part of the model is likely to differ the most / impact conclusions drawn from analysis the most?   **Comment:**  It should be emphasised that data generated for target population needs to be informative to enable the validation of extrapolation.  **Proposed change (if any):**  “… … would not be informative ***might jeopardize validation of extrapolation and*** cannot usually be supported.” |  |
| 406-407 and 419-420 | |  | | **Comment:**  Statements are partly contra dictionary. According to line 419-420 formal incorporation of historical controls is possible. But formal incorporation of this data can be interpreted also as borrowing information to an extend that generated data of target population is non-informative. That is not accepted according to line 406-407. Please clarify. |  |
| 409-410 | |  | | **Comment:**  It is our understanding that an Extrapolation Plan is to be agreed as part of a PIP. How does the Agency intend to address sample size calculations in an agreed PIP are prone to require modification due to the iterative nature of an extrapolation approach? Does the agency intend to allow greater flexibility in the KBEs related to the sample size for studies such as, “To be determined …” |  |
| 411-413 | |  | | **Comment:**  Clarification is required.  Should the possibility of change in numbers of patients in a given subgroup due to maturation of patients be taken into account? |  |
| 415-421 | |  | | **Comment:**  A preference for controlled studies is expressed but this does not consider the practical issue that paediatric trials are likely to enrol especially refractory subjects, who have failed all approved options, which makes inclusion of an (active) comparator problematic. Also the use of placebo arms is regularly not considered ethical in paediatric subjects and is not supported by many investigators (for example in IBD: Turner et al 2016:  Use of Placebo in Paediatric Inflammatory Bowel Diseases: A Position Paper From ESPGHAN, ECCO, PIBDnet, and the Canadian Children IBD Network). Indeed, one of the potential benefits of the use of an extrapolation approach is to avoid the exposure of children to ineffective comparators or placebo in studies.  Also, Randomised Controlled trials (RCTs) are mentioned, and contrasted to the formal incorporation of historical controls.  But alternatively to those two ways, an external control group (e.g. new registry) could also be generated in parallel to the conduct of the trial in the treated paediatric population.  The paper may emphasise this third option, as it has various advantageous over a historical control (current Standard of Care (SoC) and latest End Point (EP) assessments), while it may not carry the difficulty of a blinded treatment with a not necessarily well-established efficacy, or worse, the potential for an intended placebo control.  Finally, it would be helpful to provide some guidance and references on how to do it in the paediatric setting.  **Proposed change (if any):**  Add further guidance on points to consider when using historical controls  **Proposed change (if any):**  *“Choice of control group: randomised, controlled studies, double-blind where feasible, are preferable in order to provide an estimate of the active treatment effect*. ***In the absence of effective comparators or limited patient population, use of alternative approaches such as historical data, or within subject comparisons should be justified***.” |  |
| 423-426 | |  | | “For studies with an intention to extrapolate efficacy from adults to children where using PK as a bridge would not suffice, the primary endpoint that may predict outcome in confirmatory PK/PD trials should be a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives.”  **Comment:**  This sentence is misleading as PK/PD studies are not confirmatory trials. We don’t understand what is meant, please explain and revise eg as proposed.  **Proposed change (if any):**  “For studies with an intention to extrapolate efficacy from adults to children where using PK as a bridge would not suffice, the primary endpoint that may predict outcome in ~~confirmatory~~ PK/PD trials ***when used as confirmatory study,*** should be a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives.” |  |
| **Section 5.2.2** | | | | | |
| 437 | |  | | **Comment:**  Suggest using another term eg "realisation" rather than "validation". Models, methods can be validated. With the term, there may be confusion. If the realization of the "extrapolation plan" fails then the whole drug development has failed and there are a lot of implications. If a model fails validation the consequences are minor because without a validated model, no extrapolation can be performed, the model can be redeveloped until it fulfils validation criteria.  In addition, it is unclear to what extend the extrapolation concept will be considered valid (line 437). It would be helpful if methods for validation could be expanded. The pathway for a “failed” extrapolation concept needs to be further detailed. |  |
| 438-440 | |  | | **Comment:**  The title of 5.2.2 includes "validation" but this first sentence implies updating the model with the new paediatric data. |  |
| Lines 442 and 443 | |  | | **Comment:**  The phrase "the extrapolation concept needs to be updated (see section 5.2)" does not make sense in context. Section 5.2 is the extrapolation plan, not the extrapolation concept. Furthermore, “(see section 5.2)” is inconsistent with how sections have been referred to earlier in the document (see comments above regarding lines 295, 300, and 304).  Consider correcting the cross references.  **Proposed change (if any):**  "the extrapolation **~~concept~~** ***plan*** needs to be updated (see section 5.2***, Extrapolation plan***)". |  |
| **Section 5.3** | | | | | |
| 448-450 | |  | | **Comment:**  We suggest the term “minimize” risks instead of “mitigate”  **Proposed change (if any):**  A formal, structured plan to ~~mitigate~~ ***minimize*** risks and address key uncertainties during development and 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. |  |
| 452 | |  | | **Comment:**  We suspect that the word “population” is missing and the end of the first sentence  **Proposed change (if any):**  “… being generated in the target ***population***.” |  |
| 454-455 | |  | | **Comment:**  Does the same apply for long term safety outcomes? Clarification is required. |  |
| 456 | |  | | **Comment:**  In this section, we would expect the authors to explain how to communicate the extrapolation concept and plan through PIP (EMA) and PSP (FDA) regulatory documents |  |
| **Section 5.4** | | | | | |
| 456-474 | |  | | **Comment:**  The heading for this section is not consistent with phrases and wording used elsewhere in the document.  **Proposed change (if any):**  “5.4. Submission and reporting of the extrapolation **~~exercise~~** ***concept and plan***” |  |
| 472-474 | |  | | **Comment:**  Please clarify: (1) what structure/format the agency envisages to “… complement the Clinical Study Report …”. This report would not be a part of the study thus would not be appropriate to append as part of an Appendix.; (2) what variation/procedure is anticipated to submit this “report”? (3) to whom should this report be submitted (PDCO, CHMP, other)?  **Proposed change (if any):**  Once a test or trial that is part of the extrapolation plan has been completed, a***n annex could be appended*** ~~report may be submitted~~ as a complement of the Clinical Study Report, integrating the new information with existing knowledge to update – if appropriate – the extrapolation concept and plan. |  |
| **Extrapolation Framework Table** | | | | | |
|  | |  | | **Comment:**  The extrapolation framework table is complex and it is not clear how to interpret the information within the table  Sometimes ‘validation’ of extrapolation is not necessary.  What does it mean by ‘Further validation’?  **Proposed change (if any):**  Perhaps divide the table into multiple tables that are simpler to understand and more clearly link it to the relevant sections of the concept paper.  Please consider providing a decision tree.  Please provide clarification / explanation what ‘Further validation’ means.  Consider development of a document template as part of PIP for extrapolation plan with relevant sections included. |  |
| **Extrapolation Table Framework** | | | | | |
| 475-477 Table on P.14 | |  | | **Comment #1:** We agree that the sponsor should have a strong scientific argument when to claim that extrapolation is appropriate. We suggest that in addition to the table on page 14 it would be helpful to include a decision tree clearly outlining the EMA thinking. For example, if the disease is the same in paediatric populations and adults, only posology needs to be determined, along with assessment of safety. When the disease in paediatric and adults is different, then demonstration of clinical efficacy would be required. PK or PK/PD relationships, if established, may be useful in determining starting doses in such cases. Extrapolation of safety for paediatric studies may be appropriate in some situations and should be considered but it is not always feasible to quantify extrapolation of safety.  **Comment #2:**  In the 2016 version of the reflection paper, this equivalent table was referenced throughout the document.  **Proposed Change:**  Extrapolation table on the back page.  We would find this helpful rather than no references as it is now.  **Comment#3:** The extrapolation framework table does not mention the principle element in the framework, “Mitigation of uncertainty and risk.”  **Proposed change (if any):** “Mitigation of uncertainty and risk,” should be added to the table, as appropriate.  According to Section 5.3, the mitigation of uncertainty and risk should be included as part of the extrapolation plan, we suggest adding this into the row that is labelled "Extrapolation plan". Alternatively, create an additional row labelled "Mitigation of uncertainty and risk".  **Comment #4:** Further comments (a-d) on the Extrapolation framework table:   1. “Age-related differences in” under “Disease manifestation & progression” does not need the “-“ in front of it. 2. Under “Pharmacology” and “Quantitative evidence” the covariates are not displayed in a consistent manner with the other columns in that row. For example, disease is displayed as "disease, comorbidity" or "disease types, severity". 3. Under “Pharmacology” and ”Prediction” should “per paediatric subgroup” is not consistent with “by paediatric subgroup” in the other columns in that row? 4. Suggest changing “Validation & extrapolation” to “Validation of the extrapolation concept” (Please consider using a term different from ‘validation’.   **Proposed change (if any):**   1. Remove "-" from “- Age-related differences in” under “Disease manifestation & progression”. 2. Present the covariates listed under “Pharmacology” and “Quantitative evidence” consistently. For example, disease types, severity, comorbidity should all be displayed in the same way. 3. Change “per paediatric subgroup” to “by paediatric subgroup” Under “Pharmacology” and ”Prediction” for consistency with the other columns in that row. 4. Change “Validation & extrapolation” to “Validation of the extrapolation concept” |  |
| Validation & Extrapolation section | |  | | **Comment:**  Can you provide any guidance in when PK and/or PD/clinical response or disease progression is considered “different” |  |
| Column labelled Disease manifestation & progression | |  | | **Comment:**  It is not clear what is meant by the term “validation” in the context of disease manifestation and progression. The two statements “Confirm predicted differences in disease progression” and “Conclude on disease progression in target population” are ambiguous. Is it the intent that each sponsor will provide this for each drug/disease indication? Or is it that if there is a medical community consensus opinion, it will be considered adequate? It would be helpful to have some insight into the “burden of proof” required for this aspect. |  |