21 September 2018
EMA/696705/2018

Overview of comments received on ' Reflection paper on the use of extrapolation in the development of medicines for paediatrics ' (EMA/189724/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	ACRO (Association of Clinical Research Organizations)
2	AESGP (Association of the European Self-Medication Industry)
3	BPI (Bundesverband der Pharmazeutischen Industrie - German Pharmaceutical Industry Association)
4	Bristol-Myers Squibb
5	EFPIA
6	EFSPI
7	Eisai
8	EAHP (European Association of Hospital Pharmacists)
9	ECNP (European College of Neuropsychopharmacology)
10	European Crohn's and Colitis Organisation
11	European Society for Paediatric Oncology (SIOPE)
12	Ferring Pharmaceuticals
13	Gemeinsamer Bundesausschuss (G-BA; Federal Joint Committee)
14	German Society for Phytotherapy
15	International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium)
16	Institute for Quality and Efficiency in Health Care (IQWiG)
17	lead pediatric and pharmacometrics investigators at the Duke Clinical Research Institute
18	Lundbeck
19	Medicines for Europe
20	Novadiscovery
21	Vaccines Europe
22	Vertex

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I. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	ACRO welcomes the draft Reflection Paper on the use of Extrapolation in the Development of Medicines for Paediatrics. ACRO congratulates the EMA on drafting a generally comprehensive document on such a complex subject.	Accepted.
1	The term "prediction" is used throughout the draft document. However, generally, in statistics, "prediction" means a statement about data that, while not now observed, could, in principle, be observed; "inference," in contrast, is making a statement about population parameters (where the "population" is the large set from which sample(s) could be taken) that are fundamentally unknowable (except in finite population situations). However, various lines of the reflection paper mention making predictions about the target population; this is confusing. We believe that "inference" is intended, instead, since the ICH E9 guideline on Statistical Principles for Clinical Trials (§2.1.2) indicates that clinical trials endeavour to make general statements about populations, not only about study subjects.	Not accepted. The word prediction was deemed to be more appropriate to be used throughout of the document rather than inference that have a very strong statistical meaning.
1	It would be helpful to explain how the extrapolation concept and plan, and their validation, will be embedded into (or positioned along with) current regulatory procedures; for instance, when should the extrapolation concept and plan first be submitted/presented to EMA (e.g. with PIP or during SA as needed)? Also, any recommended/specified time frame for amendments to the extrapolation concept and plan and their reporting might need to be presented if their submission and maintenance are correlated to regulatory procedures.	Accepted.
1	Though the extrapolation framework table could be referenced for documentation of the extrapolation concept and plan and their validation, it would be helpful if the EMA were to produce a related template and/or guideline for use by sponsors.	Not accepted. 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

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		Party respectively.
2	We would like to take this opportunity to highlight the importance of non-interventional studies (NIS) as an instrument for the paediatric development that should be taken into consideration during the further development of the reflection paper. General Aspects The development and authorised application of medicinal products for adults provides a rich source of data regarding the efficacy and safety of a product. Extrapolation from data in adults has already been proven as a suitable tool to inform about the similarity between adults and children, reducing the required paediatric data from clinical trials necessary for the application of a medicine in the paediatric population. Gather long-standing experience from real-life usage The extrapolation as an instrument to expand existing knowledge to other age groups where the medicinal product is also suitable to be used is well described in the paper. Data collection and evaluation should also include the available experience in this field. Empirical studies based on real-life data can provide suitable options for such cases. Very often, the application of already existing products that are well-established and medicinally applied since many decades or even centuries in the paediatric population happens on an off-label basis. Many of these products with such long-standing use have a widespread off-label use (e.g. not authorised for one or more paediatric age groups) in paediatric real-life, however with few documentation; the already existing experiences with such medicinal products should not be lost. Even if the PK/PD-based approach is regarded as state-of-the-art, other tools such as empirical approaches need to be used and accepted. As a retrospective approach, the systematic collection in a scientific manner of the existing experience from previous therapeutic use in children can provide valid information on the safety and the therapeutic usefulness of such products. Prospective approaches are also possible. The use of real-life data has already been considered in the first draft of the reflection paper from 1st April 2016 that was intensively discussed during an EMA-Workshop in May 2016. It was concluded that	Partly accepted. Sections 5.1 and 5.3 have been revisited acknowledging the comment.

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	real-life data should be kept in mind. But this important aspect is no longer considered in the current version. The concept of a NIS-based iterative age extrapolation should urgently be mentioned in this reflection paper as it is particularly important for some product groups like for example herbal medicinal products. See also the following publication: Karin Kraft. Position statement evidence generation in the paediatric population–Extrapolation. Phytomedicine 2017, Volume 36: 126-127. Open access: https://doi.org/10.1016/j.phymed.2017.09.003 We therefore propose to amend the guideline text with a few sentences in chapter 4 and to include a new sub-chapter in 5.2.1.: 1) Chapter 4: Extrapolation can be used to develop new drugs but also to strengthen the application of already existing products that are well-established and medicinally applied since many decades or even centuries, in the paediatric population. Many of these products with such long-standing use have a wide-spread off-label-use (e.g. not authorised for one or more paediatric age groups) in paediatric real-life, however with few documentation; the already existing experiences with such medicinal products should not be lost. Data collection and evaluation should therefore also include the available experience in this field. Empirical studies based on real-life data can provide suitable options for such cases. 2) Include a new chapter 5.2.1.3. Real life data in the extrapolation plan The development and authorised application of medicinal products for adults provides a rich source of data regarding the efficacy and safety of a product. Extrapolation from data in adults has already been proven as a suitable tool to inform about the similarity between adults and children, reducing the paediatric data requirements necessary for the application of medicine in the paediatric population.	

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	Extrapolation can be used to develop new drugs but also to strengthen the application of already existing products that are well-established and medicinally applied since many decades or even centuries, in the paediatric population. Many of these products with such long-standing use have a wide-spread off-label-use (e.g. not authorised for one or more paediatric age groups) in paediatric real-life, however with few documentation; the already existing experiences with such medicinal products should not be lost. Data collection and evaluation should therefore also include the available experience in this field. Empirical studies based on real-life data can provide suitable options for such cases. Especially for medicine containing chemically defined compounds the PK/PD-based approach is regarded as state-of-the-art. This approach is broadly accepted as a surrogate parameter allowing to predict safe doses for the use in the paediatric population. But it requires to keep in mind that this is only one of some options available, since this approach is not suitable e.g. for locally applied medicines with local effects, vaccines or herbal medicinal products. Other tools such as empirical approaches need to be used and accepted. As a retrospective approach, the systematic collection in a scientific manner of the existing experience from previous therapeutic use in children can provide valid information on the safety and the therapeutic usefulness of such products. Also prospective approaches are possible.	
3	General Aspects To a significant extent, extrapolation - as described in the current version of the reflection paper - is focused on PK/PD data. This approach is mainly applicable for chemical defined compounds, but it should be kept in mind that it is often not suitable e.g. for locally applied medicines with local effects, vaccines, herbal and homeopathic/anthroposophic medicinal products and allergen preparations. Other tools such as empirical approaches need to be used and accepted as well. Many medicinal products, such as herbal, homeopathic and anthroposophic medicines or allergen preparations, have continually proven their efficacy and tolerability in daily use by many thousands of patients over a period of decades. That is why these therapies belong to the standard therapeutic spectrum of medical professionals and are strongly supported by pharmacists and consumers alike. This long period of experience and knowledge is of scientific value which should not be lost. Here e.g.	Partly accepted. Sections 5.1 and 5.3 have been revisited acknowledging the comment.

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	empirical studies based on real-life data can provide suitable options in many cases. Thus, we favour a more pragmatic approach where other data sources (e.g. long-term medical experience documented in surveys, pharmacovigilance data, prescription data and sales figures, real life data, etc.) are also accepted as a basis for extrapolation. In this respect we would like to point out to an interesting approach suggested by Kraft (2017): 'Concept of Conditional Approval with subsequent NIS-based Iterative Age Extrapolation of Clinical Evidence'	
3	Based on such a well-documented non-interventional study (NIS), an iterative extrapolation from the age group for which the product is already authorised and a consecutive extension of these age groups (age stag-gered approach) should be scientifically justifiable. Moreover, this is in line with the current suggestions of the EMA Scientific Guidance on PAES (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015) ex-pressively allowing observational study approaches. A "conditional approval" followed by an iterative NIS-based process may serve for sequential de-escalation of age groups in the labelling of established medicinal products over time. Such extrapolation of real-life data on established medicines can be an important alternative to the PK/PD-based extrapolation. See also: Karin Kraft. Position statement evidence generation in the paediatric population – Extrapolation. Phytomedi-cine 2017, Volume 36: 126-127. Open access: https://doi.org/10.1016/j.phymed.2017.09.003 Conclusion It can be concluded, that there is a multiplicity of data sources providing a multiplicity of options for extrapolation tools outside RCTs (Randomized Clin-ical Trials). This should urgently be mentioned in this reflection paper. Proposed change:	Partly accepted. Sections 5.1 and 5.3 have been revisited acknowledging the comment.

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	We propose to add a new sub-chapter in 5.2.1.: 5.2.1.3. Real life data in the extrapolation plan	
5	Meaning of extrapolation 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.	Accepted.
5	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.	Accepted.
5	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	Accepted.

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	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.	
5	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).	Partly accepted. Please refer to the Concept paper on the need for revision of the guideline on the investigation of medicinal products in the term and preterm neonate published in September 2018.
5	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?	Accepted.
5	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.	Accepted.
5	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,	Accepted.

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	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.	
5	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.	Accepted. 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.
5	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	Accepted.

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	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.	
5	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.	Accepted.
5	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.	Accepted.
5	Terms and abbreviations are not defined: it is recommended to include a glossary of terms and abbreviations.	Accepted.
8	EAHP overall agrees with the content of the reflection paper on the use of extrapolation in the development of medicines for paediatrics. If the reflection paper is followed, all important aspects are covered, wherefore EAHP does not have any specific comments on the text	Accepted.
9	General; In the case of mental health, there will often be many imponderables to resolve in the development of extrapolation plans. It will often be unclear which similarities and differences between populations are important (for instance, the issue of whether challenging behaviours have a comparable basis in those with intellectual disability and those without may need resolving according to intellectual level or initiating medical condition or many other circumstances). The basis on which comparability is to be assessed will often be unclear.	Accepted. Aspects related to conflict of interests are out of scope.

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	The solutions envisaged - eg "Quantitative approaches to elicit expert interpretation to integrate the available information with expert judgement" are also unclear. It follows that expert judgement – both scientific and value-based - will be required at many stages of developing and achieving an extrapolation plan. It will therefore be particularly important that potentially significant or conflicting interests are clearly understood and managed; and seen to be independent of the developer. Specific: 1) In some cases, animal data can be informative of the safety profile of a drug during development. Should considerations about how to best integrate animal data be added to the document? 2) If there are examples of especially successful extrapolations that could serve as models or exemplars, it may be useful to reference them.	
10	In general we support the extrapolation concept and principles from adult (IBD studies) into paediatric studies where specific methodology on pharmacodynamics and pharmacokinetics has been met. We hope this will then speed up the regulatory approval for new drugs in paediatric IBD populations, which, at present, follows 7-8 years after adult approval. This delay leads to widespread off label and largely uncontrolled drug use in the interim, supporting the need for a new strategic approach viz. extrapolation. It is likely that the vast majority of new IBD drugs which have been shown to have a positive effect and receive approval in adult IBD populations would be suitable for this extrapolation route to subsequent approval in children, assuming that the appropriate methodology is applied. As with any regulatory decision, the data generated in the target population using extrapolation may not be sufficient to address all uncertainties related to efficacy and safety by the time of a marketing authorisation. It will still be important to gather additional data post-authorisation to address residual uncertainties. In addition, it will be important to introduce specific clinical study design elements in trials of the adult population to inform and strengthen a future extrapolation concept for development in children. Important elements include a thorough characterization of pharmacokinetics and pharmacodynamics, and a head-to-head comparison design instead of a placebo-controlled design. We would assume the extrapolation plan would be submitted in the same way and approximate timing as the paediatric investigational plan is currently so that approval is in place prior to any paediatric studies taking place. The proposed model which takes into account the drug, method of delivery and	Accepted.

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	weight of evidence in initial adult studies would allow flexible extrapolation plans to be in place for different studies. We also support the outline of what should happen when an extrapolation plan fails. There is no mention of whether the extrapolation study relates to a drug that is 'first in class' or not. We would suggest extrapolation plans needed for a 'first in class' drug would differ from studies where the drug is not first in class or is an approved drug being given by a different route. It may be worth considering this distinction in the examples of extrapolation plans listed at the end of the document.	
11	SIOP-E welcomes the Agency's Reflection paper on the use of extrapolation in the development of medicines for paediatrics. Cancer drug development is predominantly driven by adult cancer needs but many of the drugs in development have potential application in the paediatric population. There are many situations where data already generated by studies in the adult population could be used in an extrapolation concept to avoid unnecessary replication of studies, allowing the studies conducted in the paediatric (target) population to be appropriately focused on addressing the clinically relevant gaps in knowledge. There are broadly two circumstances in paediatric oncology where extrapolation would be relevant; a) where the occurrence of a specific cancer spans the age range, for example this would include some forms of leukaemias including chronic myeloid leukaemia and acute myeloid leukaemia, some forms of lymphomas including Hodgkin lymphoma bone sarcomas, including osteosarcoma and Ewings sarcoma and melanoma. Where the disease is considerably less common in the paediatric age range, but biologically similar; i.e; chronic myeloid leukaemia or melanoma, the application of the extrapolation concept would avoid initiation of unfeasible efficacy studies that are inherently under-powered and uninformative and replace them with properly modelled extrapolations from existing (adult) data and formulation of a plan for more focused and informative data collection in the target population, for example age-range targeted PK studies.	Accepted.
11	The second circumstance is where a drug's development has been for an adult cancer, but the drug's mechanism of action has scientific relevance in a paediatric cancer. Consideration of extrapolation of information gathered in the adult studies (clinical and pre-clinical), particularly on PK vs PD relationship	Accepted.

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	and in relation to PD vs clinical effectiveness could be explored in an extrapolation concept to inform and focus the paediatric study designs. The concept of collection of follow-up data post-marketing authorization as part of a risk mitigation plan where long term events may occur in the paediatric (target) population that could impact on the risk-benefit is extremely welcome. The Reflection paper is sufficiently broad and inclusive to support the majority of circumstances where extrapolation could be of value. In subsequent supporting documents it would be helpful to see some worked examples as guidance for how these concepts could be practically applied. There may be a need for education and training programs to develop the expertise needed in this area.	
12	The document could be substantially shortened and more to the point, using clearer language. It would be valuable if a suggested table of contents, template or example of an extrapolation plan could be provided. Please provide some more detailed guidance on when in the drug development process an extrapolation plan should be submitted and how the plan relates to the PIP, considering also that the extrapolation plan should allow for refinement given emerging information (line 313). Submission timing considerations from earlier draft guidance could with advantage be used: Early regulatory review of extrapolation concept and plan is recommended (at the latest at the expected time of PIP application, but often likely earlier in view of impact on overall development program) The text differentiates between clinical response versus PD response and the difference between these should be described to improve readability.	Accepted.
13	From an HTA point of view, and with respect to a subsequent possible extrapolation of an additional benefit, the G-BA would like to make the following remark: As a basis for extrapolation, at least limited data on a clinically meaningful endpoint and safety data would be desirable for all paediatric target populations, irrespective of the available data in the source	Accepted.

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	population and the similarities in pharmacology, course of disease and clinical response of source and target population.	
14	The "Gesellschaft für Phytotherapie e. V.", i.e. Society for Phytotherapy, is the German scientific society for all aspects of the research on a therapeutic use of herbal medicinal products. It was founded in 1971 as a scientific society of physicians, pharmacists and scientists. The society supports the basic and applied research on medicinal plants and herbal medicinal products, including pharmaceutical, pharmacological and especially clinical research, including the collection, generation and assessment of scientific data and clinical experience on the use of medicinal plants, their constituents and the preparations thereof. We would like to take this opportunity to point to some important aspects that should be taken into consideration during the further development of the reflection paper. General Aspects The development and authorised application of medicinal products for adults provides a rich source of data regarding the efficacy and safety of a product. Extrapolation from data in adults has already been proven as a suitable tool to inform about the similarity between adults and children, reducing the paediatric data requirements necessary for the application of medicine in the paediatric population. Long-standing experience from real-life should not be lost Extrapolation can be used to develop new drugs but also to strengthen the application of already existing products that are well-established and medicinally applied since many decades or even centuries, in the paediatric population. Many of these products with such long-standing use have a wide-spread off-label-use (e.g. not authorised for one or more paediatric age groups) in paediatric real-life, however with few documentation; the already existing experiences with such medicinal products should not be lost. Data collection and evaluation should therefore also include the available experience in this field. Empirical studies based on real-life data can provide suitable options for such cases. There is not only one way of extrapolation	Not accepted. Conditional approval is out of scope.

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	Especially for medicine containing chemically defined compounds the PK/PD-based approach is regarded as state-of-the-art. This approach is broadly accepted as a surrogate parameter allowing to predict safe doses for the use in the paediatric population. But it requires to keep in mind that this is only one of some options available, since this approach is not suitable e.g. for locally applied medicines with local effects, vaccines or herbal medicinal products. Other tools such as empirical approaches need to be used and accepted. As a retrospective approach, the systematic collection in a scientific manner of the existing experience from previous therapeutic use in children can provide valid information on the safety and the therapeutic usefulness of such products. Also prospective approaches are possible. One approach to solve the problem: 'Concept of Conditional Approval with subsequent NIS-based Iterative Age Extrapolation of Clinical Evidence' Example: Herbal medicinal products. Due to the multicomponent character of herbal preparations, the collection of product-specific PK/PD data for use as surrogate parameters in determining a safe dose in children is in general not feasible and/or meaningless. Therefore, providing PK/PD data should not be made mandatory in paediatric research on this type of drugs. Herbal medicinal products are characterized by long-standing use with typically a broad therapeutic range and only few side effects. Based on existing similarities data from adults (>18 yrs), where available and sufficient, could be extrapolated to an adjacent age group (e.g. 16-18 yrs) and a "Conditional Approval" granted with the condition to establish further data by performing a non-interventional study (NIS). If sufficient evidence is established for the second age group these data can be extrapolated to a third group (e.g. 14-16 yrs), and so on. Based on such a well-documented non-interventional study (NIS), an iterative extrapolation from the age group for which the product is already authorised and a consecutive extension of these age groups (age staggered approach) should be scientifically justifiable. Moreover, this is in line with the current	

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	suggestions of the EMA Scientific Guidance on PAES (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015) expressively allowing observational study approaches. A "conditional approval" followed by an iterative NIS-based process may serve for sequential de-escalation of age groups in the labelling of established medicinal products over time. Such extrapolation of real-life data on established medicines can be an important alternative to the PK/PD-based extrapolation. The use of real-life data had already been considered in the first draft of the reflection paper from 1st April 2016 that was intensively discussed during an EMA-Workshop in May 2016. Even at the end of this workshop Dr. Dirk Mentzer emphasized in his conclusion that real-life data should be kept in mind. We are wondering, why this important aspect has been deleted in the current version. Conclusion As can be concluded, there is a multiplicity of data sources providing a multiplicity of options for extrapolation tools, including the concept of a NIS-based iterative age extrapolation, which need to be included in the development of extrapolation concepts, for allowing their usefulness also for important product groups like herbal medicinal products. This should urgently be mentioned in this reflection paper. See also following publication: Karin Kraft. Position statement evidence generation in the paediatric population–Extrapolation. Phytomedicine 2017, Volume 36: 126-127. Open access: https://doi.org/10.1016/j.phymed.2017.09.003 Proposed change: We therefore propose to amend the guideline text with a few sentences in chapter 4 and to include a new sub-chapter in 5.2.1.: 1) Chapter 4: Extrapolation can be used to develop new drugs but also to strengthen the application of already	

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	existing products that are well-established and medicinally applied since many decades or even centuries, in the paediatric population. Many of these products with such long-standing use have a wide-spread off-label-use (e.g. not authorised for one or more paediatric age groups) in paediatric real-life, however with few documentation; the already existing experiences with such medicinal products should not be lost. Data collection and evaluation should therefore also include the available experience in this field. Empirical studies based on real-life data can provide suitable options for such cases. 2) Include a new chapter 5.2.1.3. Real life data in the extrapolation plan General Aspects The development and authorised application of medicinal products for adults provides a rich source of data regarding the efficacy and safety of a product. Extrapolation from data in adults has already been proven as a suitable tool to inform about the similarity between adults and children, reducing the paediatric data requirements necessary for the application of medicine in the paediatric population. Long-standing experience from real-life should not be lost Extrapolation can be used to develop new drugs but also to strengthen the application of already existing products that are well-established and medicinally applied since many decades or even centuries, in the paediatric population. Many of these products with such long-standing use have a wide-spread off-label-use (e.g. not authorised for one or more paediatric age groups) in paediatric real-life, however with few documentation; the already existing experiences with such medicinal products should not be lost. Data collection and evaluation should therefore also include the available experience in this field. Empirical studies based on real-life data can provide suitable options for such cases. There is not only one way of extrapolation Especially for medicine containing chemically defined compounds the PK/PD-based approach is regarded as state-of-the-art. This approach is broadly accepted as a surrogate parameter allowing to predict safe doses for the use in the paediatric population. But it requires to keep in mind that this is	

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	only one of some options available, since this approach is not suitable e.g. for locally applied medicines with local effects, vaccines or herbal medicinal products. Other tools such as empirical approaches need to be used and accepted. As a retrospective approach, the systematic collection in a scientific manner of the existing experience from previous therapeutic use in children can provide valid information on the safety and the therapeutic usefulness of such products. Also prospective approaches are possible. One approach to solve the problem: 'Concept of Conditional Approval with subsequent NIS-based Iterative Age Extrapolation of Clinical Evidence' Example: Herbal medicinal products. Due to the multicomponent character of herbal preparations, the collection of product-specific PK/PD data for use as surrogate parameters in determining a safe dose in children is in general not feasible and/or meaningless. Therefore, providing PK/PD data should not be made mandatory in paediatric research on this type of drugs. Herbal medicinal products are characterized by long-standing use with typically a broad therapeutic range and only few side effects. Based on existing similarities data from adults (>18 yrs), where available and sufficient, could be extrapolated to an adjacent age group (e.g. 16-18 yrs) and a "Conditional Approval" granted with the condition to establish further data by performing a non-interventional study (NIS). If sufficient evidence is established for the second age group these data can be extrapolated to a third group (e.g. 14-16 yrs), and so on. Based on such a well-documented non-interventional study (NIS), an iterative extrapolation from the age group for which the product is already authorised and a consecutive extension of these age groups (age staggered approach) should be scientifically justifiable. Moreover, this is in line with the current suggestions of the EMA Scientific Guidance on PAES (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015) expressively allowing observational study approaches.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	A "conditional approval" followed by an iterative NIS-based process may serve for sequential de-escalation of age groups in the labelling of established medicinal products over time. Such extrapolation of real-life data on established medicines can be an important alternative to the PK/PD-based extrapolation.	
15	The agency is thanked for this comprehensive summary on using extrapolation concepts to guide paediatric drug development, and the effort to bring the view of many different regulatory internal stakeholders together. It appears to be the first reflection paper after the EMA commented positively on the MID3 framework, largely referring to concepts described therein and actively proposed in the paper. This document is definitely welcomed by the industry and it is acknowledged as a significant step forward in the use of extrapolation concepts within the development of medicines for Paediatric patients.	Accepted.
15	Comment: The framework contains several concepts that could 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 guidance/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. As such, we agree that more work informed by review of specific drug development programs likely needs to be done in order to develop explicit policies and regulatory guidelines around the application of some of these concepts to paediatric drug development, especially in sub-groups of the paediatric populations that are hard to study. Proposed change (if any): An appendix with examples of acceptable approaches in hypothetical or actual situations would be helpful. Please provide clarification about how the reflection paper could be updated over time as additional experience is gained with extrapolation strategies.	Accepted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
15	The reflection paper provided a number of factors to consider for extrapolation evaluation, however, it doesn't provide a clear path where to start, and how each evaluation will affect the pediatric program, i.e. what pediatric studies are needed. Please consider providing relevant information similar to the FDA's pediatric study decision tree.	Accepted. New section 6.
15	Comment: 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 section. Proposed change (if any): 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 reflection paper, it would be beneficial to clarify and provide points for consideration for each of these areas. The contents in this current version of the reflection paper seem only addressing efficacy extrapolation.	Accepted.
15	Comment: During a paediatric development program, data gathered from completed studies may help to inform the need for an extrapolation program. For example, if a sample size re-estimation is required and the feasibility becomes more challenging, an extrapolation plan developed at that point may help mitigate the difficulties in recruitment by extrapolating from adult data. Proposed change (if any): We suggest adding additional language to ensure extrapolation concepts and plans can be considered after embarking on a paediatric development program. Additional data and evidence generation during the course of the paediatric studies maybe conducive to designing an extrapolation program.	Accepted.
15	This document also appears to be isolated by itself. With the recent update of the FDA's pediatric Clinical Pharmacology guidance, ICH E11 R1 and the ongoing effort by ICH on E11 R2, it would be great if the recommendations from these documents could be harmonized.	Accepted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
15	Comment: Terms and abbreviations are not defined. Proposed change (if any): Recommend a glossary of terms and abbreviations be included.	Accepted.
15	Comment: 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). Proposed change (if any): Suggest using paediatrics throughout for consistency, then adolescents, children, infants, etc., can be used to describe specific subgroups	Accepted.
16	IQWiG appreciates the opportunity to comment on the reflection paper. IQWiG supports the revision of the "Reflection paper on the use of extrapolation in the development of medicines for paediatrics" with respect to the aim of providing a framework for extrapolation as a methodology to generate evidence for regulatory assessment. The reflection paper could be further improved by adding and clarifying important issues, e.g., the consequences of a negative outcome of the extrapolation plan, the role of the comparator used in studies of the source population and in studies of the target population, the principles of evidence-based medicine to be followed when reviewing the data underlying the extrapolation concept, and ways to improve transparency.	Accepted.
17	Extrapolation to children needs to be considered/thought of with the earliest human studies in order to make sure every trial is designed to maximize the potential for extrapolation, by collecting and validating the data elements needed (dosing, endpoints, etc).	Accepted.
18	Lundbeck would like to thank the Agency for the opportunity to provide comments on the Reflection paper on the use of extrapolation in the development of medicines for paediatrics - EMA/199678/2016. Please see general and specific comments outlined below. 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 Regulation (EC) No 1901/2006, which states that development of medicinal products for the paediatric population should be achieved without subjecting this population to	Accepted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	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. 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. Examples of acceptable extrapolation plans would also be a welcome addition to help guide sponsors, provided they do not become restrictive considering future development of science and understanding of different diseases.	
19	Medicines for Europe welcomes the opportunity to comment on the EMA 'Reflection paper on the use of extrapolation in the development of medicines for paediatrics' (EMA/199678/2016). In line with earlier input and engagement on this topic, we would like to make a few suggestions to enhance the clarity of the document, particularly in terms of scope.	n/a
20	The wording of extrapolation definition ("...for another subgroup of the population (target population...") looks like there is a single population, the one from which the studied population(s) was (were) randomly drawn and the target population is part of. This is rarely true, if not never. Most of the time, the studied populations and the patients to whom extrapolation is considered are members of different contexts, such as Americans (eg trial population), Europeans and Asians (eg considered target populations). We fear that such a definition is not precise enough to help in finding a solution to the extrapolation problem. Extrapolation issue arises because we (regulators, doctors, health actors, companies,…) want to derive a prediction of efficacy (or toxicity) from a known, limited (in size and genetic, phenotypic and environmental descriptors) and non-representative (a trial population is never a random sample) population to a ill-defined population differing from the trial population both in average and whole distributions of its descriptors. The gap is even greater for paediatric populations when the trials have been run on adults.	Partly Accepted. Data from several populations can be used to develop the extrapolation context. The definition does not preclude such options. Accepted.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Extrapolation concept: why is the concept based on the PK/PD relationship first? Rather, it should be based first on efficacy size, ie the relation between absolute benefit and patient characteristics. Such a relation is obtained through modeling (either statistical or, better, mechanistic modeling). If such modeling has not been done (it is always possible), one might have recourse to the extrapolation of the PK/PD relationship, a last resort alternative, which does not guarantee the validity of the extrapolated benefit. Modeling and simulation (M&S) is the only approach that enables to explore the "onset of effect, maintenance of 80 effect or durability of response and longer-term clinical outcomes" (Introduction).	Accepted. The Reflection Paper does not preclude such options.
21	Vaccines Europe welcomes the opportunity to review the draft Reflection Paper on paediatric extrapolation. The comments provided in this document are intended to complement the comments from EFPIA; therefore only vaccine-specific considerations are included. Vaccines Europe understands that vaccines are not out of scope of the reflection paper and therefore vaccine specificities should be reflected in the document. For vaccines, extrapolation based on immune response is often used and well accepted by regulators to avoid unnecessary large clinical studies. For instance, To extrapolate the vaccine benefit to subpopulations in which efficacy trials are not feasible (e.g. disease with low incidence in the paediatric population/subset of the paediatric population) or are unethical (e.g. placebo-controlled efficacy study in the paediatric population would in some cases not be ethical for a vaccine with a demonstrated efficacy in older age groups or when a correlate of protection has been established for the same class of vaccines) To address the diversity in terms of paediatric vaccination schedules (e.g. extrapolating data generated with the most stringent vaccination schedule) To avoid unnecessary participation of children to clinical trials (e.g. when data are available in adults and infants, it may be appropriate to extrapolate to other paediatric age groups)	Partly accepted. Vaccines are not out of scope of the reflection paper and some vaccines specific aspects have been integrated in the document to the possible extent.
22	Comment: The inclusion of information on the types of extrapolation considered would very helpful (full extrapolation vs. partial vs. none)	Not accepted. The concepts of full, partial and no extrapolation do not reflect

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Comment : The inclusion of example case studies would be very useful to help illustrate the Agency's expected approach and data requirements.	the current situation. There is a wide spectrum of approaches and study designs that may be acceptable. Examples have been added to the reflection paper.

II. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Executive Summary			
33-38	1	Comment: ACRO congratulates the working party on developing a proposed definition of extrapolation that is broad and inclusive without being meaningless. However, we recommend adding clarification that the definition encompasses both extrapolation from adult to paediatric populations and between different age subgroups within paediatric populations. Proposed change (if any): Add clarification that the definition encompasses extrapolation from adult to paediatric populations, and between different age subgroups within paediatric populations.	Accepted.
32-38	19	Comment: As stated in ICH E11 (R1) ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION, the concept of "extrapolation" is used in different ways in drug development. Therefore, this guideline defines the term as "paediatric extrapolation". Likewise, the definition of the term "extrapolation" applicable to the reflection paper should be very specific to the topic of the document which is "paediatric extrapolation". This helps to avoid any confusion with e.g. Extrapolation of Foreign Clinical Data or Extrapolation of Indication. Proposed change (if any): For the purpose of this Reflection Paper Paediatric 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	Not accepted. While the focus is on extrapolation for paediatric medicines development, the underlying principles may be extended to other areas.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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 information (types of studies, design modifications, number of patients required) needed to reach conclusions'.	
37	5	Comment: "…, additional information…" Please consider replacing "information" with "evidence generation" Proposed change (if any): …general need for, additional information evidence generation (types of studies….	Accepted.
37	15	Comment: "…, additional information…" Proposed change (if any): Please consider replacing "information" with "evidence generation"	Accepted.
40-43	1	Comment: To ensure clarity, we recommend adding examples to show what is meant by "quantitative methods". Proposed change (if any): Add examples to show what is meant by "quantitative methods".	Accepted. Please also refer to the Extrapolation Framework Table.
48-49	5	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	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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".	
48-49	15	Comment: One may not always be able to "quantify" disease, pharmacology and populations and it may not always be necessary. If the target is expressed in source and target populations, the disease occurs in source and target and compounds with similar or even different MoA have been shown to be effective in source and target populations, "quantification" would not be needed. Proposed change (if any): 'Existing information…..should be evaluated. Quantification, when feasible, may help to define similarity in disease or drug pharmacology between the source and the target population.'	Accepted.
52-55	17	Comment: The guideline suggests that following identification of important assumptions and uncertainties about the relation between dose, exposure, pharmacodynamic response and clinical efficacy based on differences between the source and target populations, an assessment can be made of whether clinical efficacy can be predicated based on other pharmacological or clinical justification. How would this "other pharmacological or clinical justification" be done? Proposed change (if any): We suggest that a guidance document be issued for this to 1) ensure standardization and consistency of submissions and 2) provide a framework to sponsors/investigators	Partly accepted. 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
55	21	Comment:	Partly accepted. Vaccines are not out of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Explicitly mention immune response in the list of parameters from which efficacy can be predicted Proposed change (if any): based on other pharmacological (such as immune response for vaccines) or clinical justification	scope of the reflection paper and some vaccines specific aspects have been integrated in the document to the possible extent.
56	15	Comment: what would be the outcome of an "assessment of the impact of identified assumptions?" Proposed change (if any): clarification is needed as to the need for sensitivity analyses to test the potential impact of erroneous assumptions.	Partly accepted. The document does address technical aspects related to sensitivity analysis, but applicants are welcome to use them to support their extrapolation approaches.
58-64	1	Comment: ACRO recommends adding to this paragraph to explain where/how the extrapolation plan should be presented (e.g., should it be included within the PIP, or a reason given in the PIP for not providing an extrapolation plan?). Proposed change (if any): Clarify where/how the extrapolation plan should be presented.	Accepted.
56-57, 257, 267-272	15	Comment: The need for structured documentation consistent with the MID3 good practices is highlighted throughout the document e.g. While not the expressed opinion of the EMA or workgroup, EMA MSWG colleagues also indicated, in a recent survey (ACOP 8), that the MID3 good practices white paper was a good starting point for a regulatory guideline and could be referenced in future guidelines. Proposed change (if any): Add MID3 good practice white paper as a reference to indicate "an" example of structured approach to documentation. This would help the reader while also	Not accepted. Reference to publications are usually not supported in regulatory guidance

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		allowing for alternative approaches to be considered.	
61-62	5	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'?	Accepted. Section 5.2.2 is now labelled "Regulatory confirmation of the extrapolation concept".
65-68	15	Comment: What uncertainty, especially on disease and disease progression, would be acceptable? Proposed change (if any): Some guidance should be given, e.g. level of uncertainty comparable to the situation of FIM trial or first exploratory trial in adult patient population could be acceptable.	Not accepted. Out of scope
67-68	5	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.	Not accepted. out of scope - this question is not extrapolation specific
67-68	17	Comment: The final guideline should give examples of the type of additional data that could be collected. E.g. electronic health records Proposed change (if any): Add examples of the types of additional data that should be collected.	Accepted. See section 5.1.1 Existing knowledge and data sources to develop the extrapolation concept
69	1	Comment: ACRO welcomes the flexibility in approach provided for in the Reflection Paper and agrees that an exhaustive list of methodological approaches is not necessary. However, we believe the utility of the document would be enhanced	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		by including some examples of the approaches that could be used for various degrees of extrapolation. Proposed change (if any): Include some examples of the approaches that could be used for various degrees of extrapolation.	
69	5	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.	Accepted.
72	5	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.	Not accepted. Please refer to the EMA extrapolation concept paper for a non-exhaustive list of examples.
1. Introduction			
82	9	Comment: short-term and long-term use Proposed change (if any): short-term and long-term use-Should be defined	Accepted.
83	1	Comment: ACRO recommends replacing the term "posology" with "frequency of dosing," given the expected metabolic differences between adults & children. Proposed change (if any): Replace "posology" with "frequency of dosing".	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
79, 84, 201, 206	5	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	Accepted.
96-99	17	Comment: This sentence appears specific for clinical trials done under health authority regulatory oversight. This standard should apply to any study that involves children. Proposed change (if any): Clarify that this applies to all studies involving children, regardless of intended regulatory/marketing application. E.g., "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, where applicable, address the requirements for regulatory decision-making."	Not accepted. This is a regulatory guideline using criteria for Marketing Authorisation. Children should not be enrol in unnecessary studies.
100-113	15	Comment: The two paragraphs discussed extrapolation in extremes (full or none) and at levels in between. This is somewhat in alignment with the FDA guideline regarding when to use full, partial and no extrapolation. Proposed change (if any): Can similar framework be adopted to guide paediatric drug development supporting global submission?	Not accepted. Please refer to ICH E11R1 for global harmonisation. The concepts of full, partial and no extrapolation do not reflect the current situation. There is a wide spectrum of approaches and study designs that may be acceptable.
100-106	17	Comment: This paragraphs seems to indicate that extrapolation will be a binary variable with only 2 outcomes, yes or no. What about including the probability of successful extrapolation using Bayesian methods?	Not accepted. There is a wide spectrum of approaches and study designs that may be acceptable. Please refer to section 5.2.1.2 Therapeutic studies in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Include the probability of successful extrapolation using Bayesian methods.	the extrapolation plan.
101-103	1	Comment: This is also the case for medical conditions that affect children but not adults. Proposed change (if any): Add "or non-existent" after "completely different."	Not accepted.
101-104	17	Comment: Suggest rephrasing this sentence to avoid ambiguity that extrapolation is not possible in neonates Proposed change (if any): In some cases extrapolation will not be justifiable where the disease is completely different in children or selected age subgroups compared to adults (e.g. neonatal disease diseases unique to the neonatal populations) or the understanding of the drug's pharmacology is insufficient	Accepted.
103-106	17	Comment: We would suggest that failure to extrapolate is always unethical, regardless of the certainty of extrapolation. Rather, the highest level of scientifically justifiable extrapolation should always be considered Proposed change(if any): "In other cases IIt is would be unethical not to extrapolate findings to children whenever possible and not just when since the understanding of the disease and drug pharmacology is so well established (e.g. when a certain exposure leads to the same clinical outcome in adult and children, such as in HIV, and for some antibacterial agents) but in all cases, using the highest level of scientifically justifiable extrapolation possible under the circumstances."	Accepted.
104-106	5	Comment:	Not accepted. Please refer to therapeutic

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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).	area or disease specific CHMP guidelines.
105	1	Comment: Since the phrase in parentheses includes antibacterial agents, "exposure" seems to refer to "exposure to the investigational product" (in which case further clinical trials will probably be obviated), rather than "exposure to the disease." However, the reference is not obvious. Proposed change (if any): Clarify whether this "exposure" is the exposure to the investigational product, or the disease, or something else.	Accepted.
109-110	5	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?	Accepted. 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
117-119	5	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.	Not accepted. The reflection paper is not a technical guidance.
121-122	15	Comment: This is not adding any information as the functions for multidisciplinary	Not accepted. It is important to keep the sentence

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		collaboration are not added. Proposed change (if any): delete "Regardless….collaboration."	
123-126	19	Comment: The reflection paper is clearly written with New Chemical Entity and new Biologicals Development in mind. Target of the applicant would be to obtain a marketing authorisation in a specific paediatric patient population for which there is currently no marketing authorisation in the EU. Extrapolation shall help to take full advantage of the existing information and data to minimize and define clinical trials in children. This context should be clearer emphasised in the scope of the document. Proposed change (if any): 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 evaluation of extrapolation approaches in development of medicines for children concerning indications for which currently no marketing authorisation exists in the EU.	Partly accepted. The scope of the document can also cover medicines for which a marketing authorisation exists. Never the less, planning for a paediatric program should not be an isolated aspect of the drug development program, but rather, should be considered an integral part in the overall planning. Hence products for which currently no marketing authorisation exists are good candidate to benefit from the extrapolation framework to its full potential.
2. Scope			
	7	Comments: Eisai considers that Health Technology Assessment bodies should be involved in the consultation on the reflection paper or/and the relevant guideline in order to obtain a common understanding on the use and need for extrapolation in the development of medicines for paediatric populations. This would be expected to contribute to the efficient development of medicines for paediatric patients, so that these can be delivered to paediatric patients appropriately.	Accepted.
126-129	5	Comment:	Partly accepted. There is a wide

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	spectrum of approaches and study designs that may be acceptable, hence the document does not specify minimum criteria for a quantitative method to be considered adequate " but it is important to justify and pre-define criteria to evaluate the success of a study.
130-132	15	Comment: It is unclear whether the PIP framework is considered here or any additional authority interaction. Proposed change (if any): it may be helpful to add: "discuss extrapolation prospectively during the first PIP submission and further when first data in the target population are available… "	Not accepted. 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.
130-132	5	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.	Not accepted. 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

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
130-133	17	Comment: We would suggest emphasizing the importance of discussing extrapolation plans with regulatory agencies with the following specifics: early in the drug development process, to ensure that early studies are designed to generate the type of data needed to allow extrapolation (e.g. collection of biomarkers); with sufficient level of detail to allow for an agreement on the permissible level of extrapolation with the regulatory agencies; repeatedly during the drug development process to allow for modification of the proposed approach based on new study findings. Proposed change (if any): "Applicants are encouraged to discuss extrapolation prospectively with regulatory authorities early in the drug development process, to ensure that early studies are designed to generate the type of data needed to allow extrapolation (e.g. collection of biomarkers) with sufficient level of detail to allow for an agreement on the permissible level of extrapolation with the regulatory agencies; and then repeatedly throughout the drug development process to allow for modification of the proposed approach based on new study findings. considering the potential for future extrapolation exercises even when designing studies to support initial MA in a source population"	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
133-134	19	Comment: The reflection paper is focusing on new developments of medicines for children. Therefore, the guidance provided is very specific. The application should be defined in the scope. The last sentence of the scope is not clear and needs a better definition or can be deleted. Proposed change (if any): Please delete this sentence: While the focus is on extrapolation for paediatric medicines development, the underlying principles may be extended to other areas.	Not accepted. There is a broad range of areas where the framework can be applied and proposals can't be listed in the reflection paper. For examples please refer to the EMA extrapolation Concept Paper.
4. General considerations			
150-153	19	Comment: As stated in ICH E11 (R1) ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION, the concept of "extrapolation" is used in different ways in drug development. Therefore, this guideline defines the term as "paediatric extrapolation". Likewise, the definition of the term "extrapolation" applicable to the reflection paper should be very specific to the topic of the document which is "paediatric extrapolation". This helps to avoid any confusion with e.g. Extrapolation of Foreign Clinical Data or Extrapolation of Indication. Proposed change (if any): 4. General considerations Paediatric extrapolation is based on information in the source population (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.	Not accepted. While the focus is on extrapolation for paediatric medicines development, the underlying principles may be extended to other areas

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
155-157	5	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?	Accepted.
158	12	Comment: Incomplete sentence (seems as something is missing between "development" and "targeting" below Proposed change (if any): Having identified the scientific questions of interest for a development…..? targeting a marketing authorisation	Accepted.
161-164	5	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"?	Accepted.
164-165	5	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.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
166	1	Comment: ACRO recommends that this sentence should be made clearer since areas where there are no gaps in knowledge should be highlighted rather than identified, given that they would support a more robust/complete extrapolation plan. Proposed change (if any): "……also highlight important aspects of the concept where gaps in knowledge do not exist and hence further data need not be generated".	Accepted.
167-169	1	Comment: It would be helpful to provide actual examples where various gaps in knowledge (e.g., PK and PD) exist and the different extents of extrapolation that are recommended to be applied to them. Proposed change (if any): Provide actual examples where various gaps in knowledge (e.g., PK and PD) exist and the different extents of extrapolation that are recommended to be applied to them.	Accepted.
167-170	4	Comment: There is no definition or guidance as to how to determine/justify that a PK metric or PD response is applicable to the target population. We can often measure the PD marker in children, but whether its increase or decrease is a true marker of efficacy as it is shown to be in adults is rarely known because the validation of markers is typically done in adults. For example, Cmin or Cavg are the most commonly used PK metrics. If Cmin is a driver of efficacy in adults, then is it reasonable to assume the same in children given similarities in the disease manifestations between adults and children. Similarly, PD markers that are relevant in adults include target engagement as a measure of pharmacologic activity and relevant disease biomarkers that correlate with efficacy in adults should correlate with efficacy in children as long as the	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		disease manifestations are similar between the two populations. Please consider adding thoughts on how to justify applicability to the target population or consider providing examples of when it could be considered applicable to the target population or not.	
168	5	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?	Partly accepted. Applicability of a model has to be evaluated in relation to the uncertainties identified in the extrapolation concept.
169	21	Comment: Include a paragraph specific for vaccines Proposed change (if any): (…) exist and further data to confirm that relationship will not need to be generated. For vaccines, extrapolation based on immune response is often used and well accepted by regulators to avoid unnecessary large clinical studies. For instance, To extrapolate the vaccine benefit to subpopulations in which efficacy trials are not feasible (e.g. disease with low incidence in the paediatric population/subset of the paediatric population) or are unethical (e.g. placebo-controlled efficacy study in the paediatric population would in some cases not be ethical for a vaccine with a demonstrated efficacy in older age groups or when a correlate of protection has been established for the same class of vaccines) To address the diversity in terms of paediatric vaccination schedules (e.g. extrapolating data generated with the most stringent vaccination schedule) To avoid unnecessary participation of children to clinical trials (e.g. when data are available in adults and infants, it may be appropriate to extrapolate to other	Partly accepted. Vaccines are not out of scope of the reflection paper and some vaccines specific aspects have been integrated in the document to the possible extent.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		paediatric age groups)	
172-173	5	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).	Accepted.
173	12	Comment: Please specify what "residual" means in this context	Accepted. 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

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			additional follow-up clinical data generated post-authorisation
174-176	5	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.	Accepted.
Lines 176-177	2	Comment: It is expected that extrapolation will apply differently to different age groups: "The extent to which extrapolation may be applied may differ between age groups of the paediatric population." It would be useful to define these age groups in this guidance. Suggested age groups could be: as per EMA Reflection paper on Formulations of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf Preterm newborn infants	Not accepted. 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.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Term newborn infants (0-27 days) Infants and toddlers (1 month to 23 months) Children (2 – 11 years) Adolescents (12 – 16 or 18 years) or as per WHO Position Paper on Paediatric Age Categories to be Used in Differentiating Between Listing on a Model Essential Medicines List for Children - http://archives.who.int/eml/expcom/children/Items/PositionPaperAgeGroups.pdf Premature Newborns < 38 weeks gestational age Term Newborns > 38 weeks gestational age Neonate 0 – 30 days of age Infant 1 month – 2 years Young Child 2 – 6 years Child 6 – 12 years Adolescent 12 – 18 year Proposed change (if any): "The extent to which extrapolation may be applied may differ between age groups of the paediatric population. Suggested age groups could be: Preterm newborn infants Term newborn infants (0-27 days) Infants and toddlers (1 month to 23 months)	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Young Child (2 – 6 years) Child (6 – 12 years) Adolescents (12 – 16 or 18 years).”	
176-177	5	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).	Accepted.
178-180	5	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.	Accepted.
178-181	1	Comment: This paragraph may appear to suggest that extrapolation to younger age groups may be relied upon to support interpolation to older groups; in other words, no paediatric studies may actually be required. It is not clear if that is the intention here. It may well be possible in some circumstances (e.g., for protein pump inhibitors, where a number of drugs are already approved in adults and children, and invasive end-points correlate well with PROs) and, if this is the intent, ACRO recommends that it is stated more clearly. Additionally, recognised age subgroups of the paediatric population should be defined by reference to the ICH E11 guideline (Clinical Investigation of Medicinal Products in the Paediatric Population). Proposed change (if any):	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Add a statement to clarify the intent of the paragraph, and refer to ICH E11 for definition of age subgroups.	
178-181	18	Comment: The terminology for 'Interpolation' is not defined per ser. Could that be elaborated?	Partly accepted. The wording has been clarified. "Confirmation of an extrapolation concept to these more extreme age or disease subsets might justifiably support interpolation to e.g. intermediate paediatric age subsets"
180-181	5	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?	Accepted.
180-181	5	Comment: The term 'Interpolation' is not defined per se. Could that be elaborated? In addition, interpolation to other paediatric age subsets might then be	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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	5	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.	Accepted.
Lines 182-183	2	Comment: "The clinical studies will need to be tailored accordingly and additional clinical studies with different objectives would be required in age subsets where use of extrapolation cannot be supported." It is assumed that the clinical studies referred to in this sentence are in the adult population, it would be useful to clearly state it. Proposed change (if any): The clinical studies in the adult population will need to be tailored accordingly	Not accepted. The clinical studies to be tailored to inform the extrapolation concept can come from other sources than adults, for example: paediatric studies in a different indication.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and additional clinical studies with different objectives would be required in age subsets where use of extrapolation cannot be supported.”	
183-186	5	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.	Accepted.
183-187	17	Comment: We believe this is an essential component to successful extrapolation of novel drugs that should be emphasized in this document as it requires planning early in the drug development process. Proposed change (if any): “It may be beneficial is essential to introduce specific clinical study design elements in trials of the adult population (e.g. additional timepoints, dose-levels or biomarker) to inform and strengthen a future extrapolation concept for development in children.”	Accepted.
184-185	5	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.	Accepted.
184-186	10	“It may be beneficial to introduce specific clinical study design elements in trials	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of the adult population (e.g. additional time points, dose-levels or biomarker) to inform and strengthen a future extrapolation concept for development in children." Comment: Could also state that the inclusion of a number of older teenagers (16-18 year olds) within the initial adult studies would facilitate this approach. In addition, studies that use or analyse drug doses in mg/kg or equivalent would enhance translation/extrapolation into children.	
190-195	5	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.	Accepted.
190-196	15	Comment: It outlines the use of prior information to facilitate the development in 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.	Accepted.
197-199	5	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	Not accepted. The sentence does not recommend to administer a sub-therapeutic dose.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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	5	"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.	Accepted.
202	5	Comment: What is meant by "quality of regulatory decision making"? Please clarify.	Accepted.
203-206	15	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.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
203-206	5	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.	Accepted.
Lines 206-207	2	Comment: Clarity on which type of additional data would be requested is needed in the following sentence: "In this case these might be addressed through additional follow-up data generated post-authorisation." Proposed change (if any): "In this case these might be addressed through additional follow-up clinical data generated post-authorisation."	Accepted.
205-207	16	Comment: We agree that uncertainties underlying the extrapolation concept might not be fully resolved by the time of marketing authorisation. However, even if extrapolation is used, a positive risk-benefit ratio should be a prerequisite for marketing authorisation. Proposed change (if any):	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"It is possible that uncertainties underlying the extrapolation concept will not be fully resolved by the time of marketing authorisation despite a conclusion of efficacy or and a positive risk-benefit ratio."	
5. Proposed Framework 5.1 Extrapolation concept: synthesising evidence to identify gaps in knowledge and to make predictions for effects in the target population			
209	5	Comment: This part would deserve a section on modelling: models are made based on assumptions, made to synthesize information and to quantify uncertainties that are 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.	Partly accepted. The section has been amended.
212-213	5	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?	Partly accepted. The section acknowledges that non-clinical evidence can also be important in understanding drug pharmacology. Specific recommendations shall be part of disease specific guidance.
213	5	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	Accepted.
214-215	9	Comment:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		body size Proposed change (if any): body size (BMI or body surface)	
215	21	Comment: for vaccines differences in pre-existing immune response linked to natural exposure to the pathogen is an important factor to be considered when extrapolating data from adults to children Proposed change (if any): size, age and maturation, drug exposure (PK), baseline immune status and their relation to pharmacodynamics response (PD)	Accepted.
219-220	15	Comment: Examples (links to literature) on 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.	Not accepted. Literature references to recommend a specific method cannot be made in the reflection paper.
219	18	Comment: Could the phrasing '(Semi) quantitative methods' be elaborated?	Accepted.
219-220	5	"(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.	Partly accepted. Literature references to recommend a specific method cannot be made in the reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
5.1.1 Evidence synthesis and predictions			
General	5	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.	Accepted.
222	5	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,	Not accepted. Comment unclear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and the variability (for example between study differences) within the target population should be assessed..	
228-232	5	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	Accepted.
228-233	15	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.	Accepted.
230-232	5	Comment: Does this mean part of the synthesis could be based upon comparing response to	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		other drugs? How similar would the drugs have to be? Please clarify.	
233-237	17	Comment: We would suggest adding physiologically based PK modeling as an additional quantitative method that can be used to characterize PK differences between source and target populations. Proposed change (if any): Characterization of PK and PD: modelling relevant data (in-vitro, animal and clinical data) using for example empirical population PK/PD, physiologically based PK modelling, systems pharmacology or mechanism-based approaches 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 and organ maturation).	Accepted.
237	21	Comment: Include a paragraph specific for vaccines Proposed change (if any): Identification of a correlate of protection or demonstration that the immune response is predictive of vaccine efficacy.	Not accepted. Vaccines are not out of scope of the reflection paper and some vaccines specific aspects have been integrated in the document to the possible extent.
238-241	5	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.	Not accepted. Reference to publications are usually not supported in regulatory guidance.
238-241	5	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	Partly accepted. Wording clarified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
238-241	1	Comment: More information on Agency expectations would be beneficial here. Proposed change (if any): We would suggest a follow up guidance document specifying the expectations for qualifications of models in these two scenarios.	Partly accepted. Wording clarified
240	12	Comment: "differ" is unspecific and some words seem to be missing after "to those for" Proposed change (if any): write "be lower than" if that is meant and "to those for qualification of".	Accepted. Wording clarified.
243	1	Comment: The distinctions between Bayesian & frequentist statistics do not relate to the "precision of estimated effects;" estimates in either paradigm can be stated to any number of decimal places. Rather, Bayesian statistics (unlike frequentist statistics) can quantify certainties about population parameters. Proposed change (if any): Replace the text with "…for quantification of certainties about population treatment effects."	Partly accepted. Wording clarified.
245	1	Comment: Given that there will be no single expert interpretation, ACRO recommends revising the text, as indicated below, to reference expert opinion instead. Proposed change (if any):	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Replace existing text with "…to elicit expert opinion and to integrate that opinion with the available information could be considered…"	
245-247	15	Comment: Statement is unclear. Proposed change (if any): Please provide further clarification on 'quantitative approaches to elicit expert interpretation to integrate the available information with expert judgement could be considered as part of the extrapolation exercise'. Does it mean that expert opinion could be used to formulate the prior information under the Bayesian framework? 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.	Partly accepted. Reference to publications is usually not supported in regulatory guidance.
245-247	5	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	Not accepted. - Reference to publications are usually not supported in regulatory guidance. - 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.
253-257	5	Comment: In this evidence synthesis and prediction section, safety information is introduced; however, safety information is critical in establishing a benefit-risk	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
253-258	15	Comment: The pertinent points related to additional considerations with respect to safety are worthy of a separate section. Proposed change (if any): Suggest that a separate section be considered to highlight differences related to safety aspects. We also recommend adding a statement in the Executive summary highlighting the role of safety information and extrapolation.	Accepted.
254	12	Comment: Extrapolation may be perfectly valid if drugs have similar mechanism of action. Proposed change (if any): add "or similar" after "same"	N/A. Sentence removed.
255-257	1	Comment: ACRO welcomes the recognition that the potential impact of drugs on growth, development and maturation may not be amenable to this approach.	Accepted.
255-257	10	Comment: We agree that safety information is likely to be needed in the target population and cannot necessarily be derived from safety information in other paediatric disease areas.	Accepted.
255-258	11	Comment: The assumption that growth and maturation effects are a potential risk needs to be considered in the context of the mechanism of the drug and pre-clinical models and additional studies in children to evaluate this risk may not always be	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relevant Proposed change (if any): generation of new safety data are often likely may be needed in the target population	
257	16	Comment: We agree that it is likely that the generation of new safety data will often be required in the target population. However, it remains unclear what kind of data is expected. In addition, it remains unclear as to how a risk-benefit ratio using data on benefits and harms from different sources can be determined. Proposed change (if any): Please specify the kind of data expected for safety and the determination of the risk-benefit ratio using data from different sources. This should be supported by detailed examples (see also next comment).	Accepted.
5.1.2 Assumptions and uncertainties in making predictions			
258-282	15	Comment: On Assumptions, 5.1.2: Capturing a huge amount of various sources for uncertainty in a systematic way is well laid out. The concept on assumption handling is well reflected upon, although it will need to be seen, how it can feasibly be implemented. It will need a consolidated effort to agree on the level of evidence based on assumptions which would need to be enhanced/substituted by future evidence. Even more challenging is the case when untestable assumptions will likely be maintained through the development, and a sponsor/regulatory agreement is essential upfront to pursue a particular development path, acknowledging final interpretation still being based on considerable extrapolation then. Proposed change (if any): None	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
261-278	17	Comment: More information on Agency expectations would be beneficial Proposed change (if any): We would suggest a follow up guidance document detailing the expectations of reports submitted to EMA including these assumptions and uncertainties. This will speed up the submission of extrapolation plans that include quantitative methods.	Not accepted. 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
264	1	Comment: It is not clear whether "source data" (which the draft does not define earlier) are data collected from the source population. Proposed change (if any): Clarify the origin of the "source data."	Accepted.
270-272	5	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	Not accepted. Publications are usually not supported to be part of regulatory guidance.
270-272	18	Comment: The five main areas of assumptions are mentioned here. This seems like a key statement, we propose to highlight this more	Accepted.
271	15	Comment: What is meant by "existing data?" Proposed change (if any): "existing clinical data of drug use in the reference and potentially also the	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		target population.”	
273-282	5	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…’	Not accepted. The current wording of the text does not preclude the use of Bayesian framework.
5.2 Extrapolation plan			
283-325	17	Comment: Will PK and safety studies always be required in children or can safety also be extrapolated as long as it meets regulatory requirements for extrapolation? This section is unclear. Proposed change(if any): We would suggest clarifying if the extrapolation plan can include efficacy and safety outcomes or just efficacy.	Accepted.
284-285	5	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.	Accepted.
291-303	16	Comment: We agree that the need for data to be generated lies on a continuum, while some general scenarios can be outlined for illustration. For better understanding and illustration, generic examples covering the different scenarios should be added (similar to the generic example in the ICH E9 (R1)	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		addendum on estimands). Proposed change (if any): Add generic examples. These examples should cover a broad spectrum of scenarios, and should include positive as well as negative outcomes of the extrapolation plan. Ideally, the scenarios should be based on real cases. The description should include the extrapolation plan itself, the results of the studies covered by the extrapolation plan, and the regulatory outcome.	
295, 300 and 304	5	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)".	Accepted.
296-304	5	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	Accepted.
303-304	5	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.	Not accepted. See section 5.2.1.1 and 5.2.1.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
305	5	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.	Accepted.
305-312	17	Comment: More information on Agency expectations regarding what may be "acceptable" surrogate endpoints would be beneficial Proposed change (if any): We would suggest explicitly stating how a surrogate endpoint or biomarker would be considered acceptable (e.g. having 'enough' validation) for these purposes.	Accepted.
308	5	Comment: "6 minute walking test" example is useful but greater context is required to indicate what this relates to. Proposed change (if any):	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Add more information with respect to the example e.g. in a manner utilised effectively in lines 296-304	
309-312	16	Comment: It should be clearly stated that when using surrogate outcomes, these have not only been validated in the source population, but are also valid for the target population. Proposed change (if any): "It may be possible to use surrogate or intermediate clinical endpoints for studies in the extrapolation plan, providing that they are also valid for the target population and that they account for the physiologic developmental changes in the paediatric population."	Accepted.
310-311	5	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.	Accepted.
Line 312	2	Comment: Although it is assumed that, there is no obligation to confirm clinical benefits in the paediatric population if an endpoint is an accepted surrogate, a clarification would be helpful. Proposed change (if any): "If an endpoint is an accepted surrogate, there is no obligation to confirm	N/A. sentence removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical benefits in the paediatric population."	
319	5	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.	Accepted.
320-321	5	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.	Accepted.
322-325	1	Comment: This sentence states "The benefit of a staggered approach across age groups, due to safety concerns or the need to have PK and PD information in older children before enrolling younger children, should be balanced against the need for timely access to a medicinal product even for the youngest age groups of the paediatric population." However, the draft guidance on Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors published by the European Commission in June 2016 notes (correctly, in ACRO's view) that "a 'staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended." ACRO recommends that the current draft Reflection Paper should be aligned with the position of the expert group	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		responsible for the Commission's draft guideline. Proposed change (if any): Replace the statement with that developed by the European Commission's expert group.	
322-325	10	Comment: we strongly agree with this point and concept	Accepted.
5.2.1 Design of studies in the extrapolation plan			
327-334	1	Comment: This section appears to be suggesting the conduct of mechanistic, non-efficacy trials in children. If so, this raises ethical issues and would result in studies which could be very challenging to enrol, due to parents being reluctant to give their consent. Proposed change (if any): The intent of the text should be made clearer, and the statement aligned with the ethical principles adopted by the expert group working on the European Commission guideline referenced above.	Accepted.
5.2.1.1 Pharmacokinetic studies and Pharmacokinetic / Pharmacodynamic Studies in the extrapolation plan			
340- 341	5	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):	Partly accepted. For model qualification, qualification guidance should be followed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
340- 342	15	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?	Accepted.
340-341	11	Comment: Whilst we support this statement, it will be important within the extrapolation plan to avoid repeating unnecessary multiple dose escalations in a paediatric study when the therapeutic index would indicate that it is unlikely that unexpected toxicity would occur in the target population when dosed according to the source population data MTD.	Accepted.
341-344	5	Comment: Extrinsic factor that can affect the predictions should be considered. Proposed change (if any):	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	Accepted.
347-349	21	Comment: Include immunogenicity studies to address vaccine specificities. Proposed change (if any): Exploratory PK/PD or immunogenicity dose ranging or dose finding studies in one or several paediatric age ranges; PK or PK/PD or immunogenicity studies that aim to confirm inferred exposure levels in one or several paediatric age ranges.	Not accepted. Vaccines are not out of scope of the reflection paper and some vaccines specific aspects have been integrated in the document to the possible extent.
351	1	Comment: The sentence seems to be incomplete Proposed change (if any): Change text to "…Every effort should be made to design and power the studies to meet their objectives."	Accepted.
351-352	5	Comment:	Not accepted. To be discussed at

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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?	product specific level.
352-353	5	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)".	Accepted.
352-353	15	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. Proposed change (if any): "Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (CHMP/EWP/147013/2004)".	Accepted.
354	5	"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.	Accepted.
356- 361	5	Comment: What are EMA opinions of the minimal success criteria to support extrapolation	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		exercises? In other words what is the equivalence threshold metrics that sponsor should strive for?	
362-363	15	Comment: How likely is it that established PK/PD is identical before the PK study? Matching exposure and doses will be derived from the PK/PD study (or studies). Proposed change (if any): Delete "for example… to adults and children."	Not accepted. To be discussed at product level.
362-363	5	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, 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.	Not accepted. To be discussed at product level.
362-363	22	Comment: The paper is written at a high level, with few examples provided. The paragraph encompassing lines 362-373 is helpful because it provides concrete examples to illustrate the points made in the previous paragraph (lines 356-361). Including more examples like this one in the document would be very valuable.	Accepted.
362-364	1	Comment: The underlying assumption here is that a dose of X generates a plasma concentration of Y and that produces a clinical response of Z, all of which can be confirmed in adults, and so the same relationships will be present in children. However, this assumption should be made only when there is compelling evidence that the same relationship exists in all age subgroups of the paediatric	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		population. Proposed change (if any): Revise the sentence to read "For example, if based on the extrapolation concept the exposure-response relationship is established to be identical in adults and relevant paediatric subgroups, 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."	
364-368	5	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.	Not accepted. The sentence is important and if the powering is not feasible, applicants are encouraged to justify their approach.
365-367	15	Comment: Regarding the statement that, "…the PK study should be powered to meet a pre-specified and justified equivalence margin." Serious consideration should be given regarding the difficulties of recruiting sufficient numbers of younger age paediatric patients into single-dose intensive PK studies across many adult-approved disease indications. Sample sizes may be very small (e.g., N=6-12), which would preclude powering to meet equivalence margins. Rather, the PK can be compared with adult data empirically or using a PK/PD approach to confirm similar predicted exposures (and response, if applicable) in paediatrics vs. adults. Proposed change (if any): "Ideally, the study should may be powered to meet a pre-specified and justified	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		equivalence margin, based on feasibility of recruiting sufficient numbers of paediatric patients across the relevant age groups."	
366-367	5	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".	Not accepted. Out of scope - too detailed
372-373	17	Comment: Is this sentence suggesting that sample sizes can be reduced and used as confirmatory of model predictions? Proposed change (if any): Clarification of this point	Accepted.
374-382	17	Comment: There are other design consideration for pediatric PK PKPD studies that we would suggest including here. Suggested additions to design considerations are listed below. We would also suggest addressing the use of electronic health record and real world data to supplement clinical trial data. Proposed change (if any): Design considerations : There is a wide spectrum of approaches and study	Partly accepted. The current wording of the reflection paper does not preclude the design considerations suggested.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		designs that may be acceptable to explore or confirm an adequate dosing rationale or assumptions of the extrapolation concept. Design consideration for pediatric PK PKPD studies include: - use of sampling windows to allow for synchronization of PK sampling with standard of care lab draws - stratified enrollment by sample collection schemes that result in coverage of all necessary sampling times (windows) while limiting the number of samples drawn for each subject - availability of low volume assays - consideration for non-standard sample matrices (e.g. dried blood spots) - inclusion of a minimal number of subject per subgroup to allow for characterization of ontogeny across the pediatric age range - careful consideration of the inclusion of premature infants as a separate age group from full term infants.	
374-383	17	Different age cohorts can be enrolled in parallel or sequentially when justified, i.e from older to younger children, in paediatric PK or PKPD studies. Usually the dose regimen tested in children is the one predicted to give similar exposure or response to adults. 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. 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 children. Electronic health record and real world data may be used to supplement clinical trial data.	Partly accepted. Please refer to section 5.1.1.
378-379	5	” 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	Not accepted. Sentence to lengthy.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		children, the exposure-response for a drug is not known, you may be able to assume it is 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 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. 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…"	
377-380	5	"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	N/A. Sentence removed in the new version.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
Lines 378-380	2	Comment: It is unclear in the following sentence whether "dose level" means "dose regimen" or "doses": "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." This may need to be defined based on PK and/or dosing data obtained from adults. Proposed change (if any): "However, more dose level regimen 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."	Accepted.
383	11	Comment: This is an important point: where possible, incorporating the PK/PD studies within a confirmatory efficacy study is an efficient approach but may require an adaptive trial design.	Accepted.
5.2.1.2. Therapeutic Studies in the extrapolation plan			
385	5	Comment: Why the term "therapeutic" and not "clinical"?	Not accepted. Both section 5.2.1.1 and 5.2.1.2 are referring to clinical studies.
385	5	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	Not accepted. If the level of evidence is higher for an extrapolation plan than a standalone demonstration of efficacy, extrapolation would not be proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
393-396	18	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)?	Accepted. 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
392-396	1	Comment: ACRO welcomes and fully supports this insistence on not artificially amending study objectives.	Accepted.
392-397	6	Comment: It is unclear what is meant by "adequately powered" here? Adequately powered so that the study shows a statistically significant result or adequately powered so that the study meets a pre-defined success criteria, eg [Prob (treatment difference)>x]>y%? Doesn't the latter make more sense when there are feasibility constraints around sample size? And also what is an adequate power (90%, 80%, ...)? Of course the success criteria should not be artificial in order to line up with a certain sample size. However, the success criteria that could be met with a feasible sample size should be discussed with regulators to reach agreement on (i) the definition of the success criteria and (ii) the probability of meeting this	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		success criteria.	
393-396	5	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)?	Partly accepted. In any case, unless scientifically justified, extrapolation can't be used to address feasibility restrictions; however extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources. This situation should be considered separately for a structured and transparent approach. This discussion is seen as a relevant background to a discussion on the scientific validity of the extrapolation concept.
394-401	22	Comment: There appears to be an inconsistency between lines 394-396 and lines 399-401. In lines 394-396, we are advised not to artificially amend study objectives or success criteria to support a sample size calculation. In lines 399-401, we are advised that it is acceptable to relax the success criteria to support a sample size that has been justified, for example using a higher significance level or a wider non-inferiority margin. Because the sample size justification may involve the significance level or the NI margin, the two statements seem inconsistent. Please clarify.	Not accepted. The Reflection Paper clearly delineates between arbitrary relaxing of criteria to attempt to justify a smaller sample size, and using scientific information to justify a relaxing of criteria that leads to a smaller sample size.
399	1	Comment:	Not accepted. The purpose of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The EMA Guideline on the Choice of Non-inferiority Margin states "the most common aim of non-inferiority trials" is probably "to provide data to show that there is no important loss of efficacy if the test product is used instead of the reference." Thus, the NI margin should be selected to support showing that "the test product is not substantially inferior to the reference." If a NI margin is widened beyond such an "important loss of efficacy," as seems to be suggested here, then the analysis might fail to show the lack of that level of inferiority. Proposed change (if any): Delete the reference to "widening a non-inferiority margin".	extrapolation exercise when performing an actual efficacy study is to use the source data to justify that a lower hurdle can be crossed without the lowering of regulatory standards. Using a wider than usual margin is clearly one way of doing this
397-401	5	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.	Not accepted. This will always be on a case-by-case basis and no related guideline exists.
400	18	Comment: Would joint modelling of pooled (adult and other paediatric trial) data be an acceptable approach as well?	Accepted.
400	5	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:	Partially accepted. The first sentence is completely endorsed, and this is indeed the purpose of the Reflection Paper. The metric that is used to define success should ideally be agreed with regulators in advance, but it is beyond the scope of this document to define precisely what that metric should be, and what level

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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…"	needs to be attained.
401	5	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).'	Accepted.
404-405	5	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.	Accepted.
405-406	17	Comment: Would external data source include third party payer information and electronic health records? Proposed change (if any): Additional information regarding what EMA considers appropriate/acceptable "external data sources"	Not accepted. out of scope
406-408	5	Comment: Please specify what "extent that data generated in the target population would	Partly accepted. Data generated for target population needs to be

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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."	informative to enable the regulatory confirmation of extrapolation. For limitations please refer to section 5.1.3.
406-409	15	Comment: It is unclear what is meant here. Data in the target population would be at least confirmatory. This is contradicting the concept of extrapolation that in the extreme no uncertainties and gaps exist and no target study would be necessary. Proposed change (if any): Delete the sentence.	Partially accepted. It is undoubtedly the intention that that in the extreme no uncertainties and gaps exist and no target study would be necessary. However this covers the case where a study in the target population is required. So by definition, the prior must have a degree of uncertainty in it that requires data to be generated before a conclusion can be reached.
406-407 and 419-420	5	Comment: Statements are partly contradictionary. 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.	Not accepted. If only historical controls are borrowed, then there is no estimate of treatment effect and thus data is needed in the test arm (and possibly control arm as well) in order for a conclusion to be reached.

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409-410	5	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 …"	Not accepted. Out of scope.
411-413	5	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?	Not accepted. To be discussed within a product application.
412	1	Comment: It is not clear whether the "stratification" here refers to stratifying the randomization or the recruitment of patients, or (perhaps) both. Proposed change (if any): Clarify what "stratification" refers to in this context.	Accepted. Stratification is referred to and statistically this is with respect to randomisation. In order to clarify that this may also refer to patient recruitment, this is additionally clarified in lines 412-413.
415	15	Comment: In the discussion on "Choice of control groups" RCTs are mentioned, and contrasted to the formal incorporation of historical controls. But alternatively to those two methods, an external control group (e.g. registry) could be generated in parallel to the conduct of the trial in the treated paediatric population. The paper should consider this third option, as it has several advantages over a historical control (current SoC and latest EP assessments). Proposed change (if any): Please consider alternative approaches.	Partly accepted. Please refer to section 5.1.1
416	1	Comment: The control treatment, and not only the investigational one, could be "active"	Partially accepted. Investigational treatment is clearer wording. Although

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		(line 416). Additionally, FDA guidance on non-inferiority studies suggests that ratio measures of effect (odds ratios, risk ratios & so on) often provide a better basis for extending results of historical studies to a new NI study (less inter-study variability in treatment effects). ACRO recommends that the Reflection Paper should describe how the same principle applies to extending results from adult populations to paediatric populations. Proposed change (if any): Replace "active treatment" with "investigational treatment" in line 416, and add text to describe how ratio measures of effect can be applied to extrapolating results from adult populations to paediatric populations.	FDA guidance suggests ratio effects, the "the majority of the document uses the example of the absolute difference between treatments to illustrate the ideas. The discussion is also applicable to studies considering a relative effect with a few modifications." See EMEA/CPMP/EWP/2158/99 for further details
415-418	16	Comment: One important aspect is omitted in the draft of the reflection paper: In cases where placebo controls are inappropriate for regulatory decision-making, the role of the active comparator has to be addressed in the extrapolation concept and the extrapolation plan. Proposed change (if any): Line 418: "… from baseline within two different patient populations. If different active comparators are appropriate for the source and the target population, the consequences have to be addressed in the extrapolation plan and the extrapolation concept. If active comparators do not differ between the source and the target population, the extrapolation of effects for the comparator has to be addressed."	Partly accepted. The comment is acknowledged but the proposed wording is not agreed.
415-421 (1/2)	5	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	Partly accepted. Please refer to section 5.1.1

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		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.	
415-422 (2/2)	5	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."	Partly accepted. Further guidance on historical control has been added to the section.
419-421	1	Comment: ACRO recommends referencing the ICH E10 guideline on Choice of Control Group in this paragraph. Proposed change (if any):	Accepted. All studies in the extrapolation plan should conform to applicable legislation and recognised international methodological and ethical standards for

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Add reference to the ICH E10 guideline.	research.
419-421	15	Comment: Given the challenges in paediatric drug development, use of historical controls may be of a particular value in certain situations. 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.	Accepted.
423-426	5	"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."	Accepted.
5.2.2. Validation of the extrapolation concept			
	7	Comments: Eisai believes that it is beneficial if real world evidence (RWE) could be used for both source and target populations, as well as existing knowledge and clinical data, in the development of an extrapolation plan. The extrapolation concept can be constructed using RWE and such a concept could be validated on a case	Partly accepted. Please refer to sections 5.1.1 and 5.3.

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		by case basis. This is particularly important for less prevalent diseases.	
437	5	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.	Accepted.
438-440	5	Comment: The title of 5.2.2 includes "validation" but this first sentence implies updating the model with the new paediatric data.	Accepted.
440	17	Comment: More information on Agency expectations would be beneficial Proposed change (if any): We would suggest inclusion of criteria of what EMA would consider 'valid'.	Accepted.
438-446	16	Comment: We agree that in the case of a positive outcome of the extrapolation plan the use of extrapolation can be considered valid (line 440). However, it should also be stated that in the case of a negative outcome the use of extrapolation cannot be considered valid. Proposed change (if any): Line 442: "…, or for efficacy, cannot be confirmed, the use of extrapolation to	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		support regulatory decision-making cannot be considered valid for the time being. The extrapolation concept needs to be updated to reflect …"	
442-443	5	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)".	Accepted.
5.3 Mitigation of uncertainty and risk			
447-455	16	Comment: We agree that a structured plan to address uncertainties in the post-authorisation setting should be part of the extrapolation plan. It should however be added that a clear-cut hypothesis is also needed for post-authorisation data. In the case of a "negative" outcome of post-authorisation studies (e.g. the uncertainties cannot be resolved by these data) the marketing authorisation should be reconsidered. Proposed change (if any): Line 455: "… to document longer-term efficacy outcomes. The generation of post-authorisation data should follow a clear hypothesis and robust study design (e.g., a comparative study with an appropriate comparator and appropriate measures to avoid selection bias) to address the remaining uncertainties and assumptions underlying the extrapolation concept. Depending on the outcome of the post-authorisation studies, the marketing authorisation	Partly accepted. The comment is acknowledged but the proposed wording is not agreed for a reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		might be reconsidered."	
448-450	5	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.	Accepted.
451	1	Comment: It is not inevitable that less data will be generated in these circumstances. Even when more confidence exists in the extrapolation concept, more data might be sampled from the target population if, for example, those data are easily obtained. Proposed change (if any): Replace "inevitably" with "often".	Accepted.
452	5	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."	Accepted.
454-455	1	Comment: Upon marketing authorisation, the "longer-term efficacy outcomes" of interest are population parameters (or future data), not sample statistics; hence, trialists cannot "document" them, but, at best, can make inferences (or predictions) about them. Proposed change (if any):	Not accepted. Section revisited.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Replace "to document" with "to substantiate trustworthy inferences (or predictions) about."	
454-455	5	Comment: Does the same apply for long term safety outcomes? Clarification is required.	Partly accepted. Section revisited.
455	9	Comment: "longer-term"- efficacy outcomes Proposed change (if any): longer-term: Should be defined	Accepted.
5.4 Submission and reporting of the extrapolation exercise			
457-461	16	Comment: We propose that principles of evidence-based medicine have to be followed when developing an extrapolation concept. Proposed change (if any): Lines 458: "When developing an extrapolation concept and plan, … from the source and the 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."	Accepted.
456-474	5	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"	Accepted.
456	15	Comment: The heading for this section is not consistent with phrases and wording used elsewhere in the document.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "5.4. Submission and reporting of the extrapolation exercise concept and plan"	
456	5	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	Accepted.
458-459	12	Comment: The term "Source data" has a specific meaning in drug development. Proposed change (if any): Replace "source data" with "data from the source population".	Accepted.
468-474	22	Comment: Section 5.4, particularly lines 468-474, discusses submission and reporting of the extrapolation exercise. It is not clear, however, exactly how the Extrapolation Concept or the Extrapolation Plan should be submitted. The paper suggests that the framework can be used when presenting at regulatory procedures, like PDCO, but it is not clear what regulatory process to follow to submit it for review by regulators. It would be helpful to clarify the submission and review process.	Not accepted. 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
470	1	Comment: Not everyone reading the Reflection Paper will be familiar with acronyms commonly used within the EMA. ACRO therefore recommends that the acronyms (PDCO, SAWP, CHMP) should be defined. Proposed change (if any): Define the acronyms.	Accepted.
472-474	16	Comment: For marketing authorisations using extrapolation, the extrapolation plan (and its updates) and the data generated within the extrapolation plan are of equal	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		importance. Therefore, the publication of the extrapolation plan should be mandatory. We propose to publish the plan as part of clinical study reports (e.g. as an appendix) of trials conducted within the extrapolation plan and also as part of the EPAR. Proposed change (if any): Line 474: "… to update – if appropriate – the extrapolation concept and plan. Independent of this, the (updated) extrapolation plan should be part of the clinical study report (CSR). The extrapolation plan will be published after marketing authorisation as part of the CSR and as an appendix to the European Public Assessment Report (EPAR)."	
472-474	5	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, an 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.	Accepted.
Extrapolation Framework Table			
475-477	5	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	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
475-478	5	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".	Accepted.
475-478	5	Comment #4: Further comments (a-d) on the Extrapolation framework table: a) "Age-related differences in" under "Disease manifestation & progression" does not need the "-" in front of it. b) Under "Pharmacology" and "Quantitative evidence" the covariates are not displayed in a consistent manner with the other columns in that row. For	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		example, disease is displayed as "disease, comorbidity" or "disease types, severity". c) Under "Pharmacology" and "Prediction" should "per paediatric subgroup" is not consistent with "by paediatric subgroup" in the other columns in that row? d) Suggest changing "Validation & extrapolation" to "Validation of the extrapolation concept" (Please consider using a term different from 'validation'. Proposed change (if any): a) Remove "-" from "- Age-related differences in" under "Disease manifestation & progression". b) Present the covariates listed under "Pharmacology" and "Quantitative evidence" consistently. For example, disease types, severity, comorbidity should all be displayed in the same way. c) Change "per paediatric subgroup" to "by paediatric subgroup" Under "Pharmacology" and "Prediction" for consistency with the other columns in that row. d) Change "Validation & extrapolation" to "Validation of the extrapolation concept"	
Validation & Extrapola-tion section	5	Comment: Can you provide any guidance in when PK and/or PD/clinical response or disease progression is considered "different"	Accepted. Please refer to the new section 6.
Column labelled Disease manifesta-tion & progression	5	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.	Accepted. Wording amended in line ith the new version of the reflection paper and section 5.2.2

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	1	Comment: Mechanisms presented under clinical response to treatment seem incorrect when considering the listed items along with those under the other categories. Proposed change (if any): It may need to be corrected as "Age-related differences in - applicability - validation of efficacy & safety endpoints"	Accepted.