



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Paediatric Committee (PDCO)
Committee for Medicinal Products for Human use (CHMP)

Overview of comments received on ' Concept paper on extrapolation of efficacy and safety in medicine development' (EMA/129698/2012)

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

Stakeholder no.	Name of organisation or individual
1	European Federation of Pharmaceutical Industries and Associations (EFPIA)
2	Laboratoire du Fractionnement et des Biotechnologies (LFB)
3	CHTE – National Institute for Health and Clinical Excellence (NICE)
4	Innovative Therapies for Children with Cancer (ITCC)
5	Biogen Idec
6	European Vaccines Manufacturers (EVM)
7	European Generic Medicines Association (EGA)
8	MRC North West Hub for Trials Methodology Research
9	GRIP (Global Research in Paediatrics) Network of Excellence



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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	<p>EFPIA welcome the publication of this important and well-addressed concept paper and the opportunity to comment on it with a view to develop a framework for extrapolation approaches that are scientifically valid and reliable to support medicine authorisation.</p> <p>EFPIA consider this document a major step towards a future reflection paper on this very important topic. The EMA is to be applauded for working to bring scientific rigor and develop a clearly stated algorithm for extrapolation, given the great interest in this area, yet the risks involved.</p> <p>Nevertheless EFPIA have identified some issues that should be worth considering:</p> <p>1. The Scope of the future Reflection Paper: given the various areas where extrapolation can be used, it would be beneficial to clearly define the scope (e.g. inclusion of biologics, vaccines, biosimilars?) of this framework on extrapolation.</p> <ul style="list-style-type: none"> • Application: Many parts of the document are focused – explicitly or implicitly – on extrapolation between populations. However, it is intended to discuss also extrapolation between compounds, devices, etc. (as suggested in the third paragraph in Section 3: “all areas of medicine development”). Further examples would include the extrapolation of results for surrogate variables to target variables, extrapolation from one regimen to another, and use of a weight-adjusted instead of a fixed dose. It is not always clear whether these situations can be considered in a comparable way. For example, would this reflection paper also apply to the development of a generic drug or to the demonstration of biosimilarity? 	<p>Partly accepted. See below</p> <p>The scope will be clearly defined. The main focus of the reflection paper will be on extrapolation between age groups with an emphasis on the paediatric population.</p> <p>It will be important to keep the reflection paper to a manageable length. The scope will define the limits of the paper which may not cover all of the examples given in the comments.</p>

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	<p>Would it apply to the extrapolation between medicines, such as between drugs acting on the same target e.g. the many anti-tumour necrosis factor alpha biotherapeutics?</p> <ul style="list-style-type: none"> • Interpolation versus Extrapolation: Clear definitions of inter- and extrapolation are essential. Model-based interpolation between doses could also be considered in scope: e.g. when a mid-dose provides a marginal QTc signal whereas the adjacent doses do not. • Efficacy/Safety: In what situation can extrapolation based on efficacy, but also surrogate markers be considered: e.g. label claims on special populations, clinical doses not fully studied in phase 3, or more restricted as bases for subsequent study design of phase 2b and 3? • Although "Safety" is mentioned in the title of the concept paper, it is not emphasized in the body of the text. It would be beneficial to understand the role of extrapolation in this context. <p>2. The paediatric experience, its value and weaknesses: much of the concept paper relies on the paediatric experience as a model for how extrapolation can be approached. However, in that experience one is usually extrapolating within the same disease and using the same drug. The same could apply to other important patient populations who are not addressed and are likely to benefit from extrapolation studies, such as the elderly patients [see ongoing discussion on the use of M&S in the geriatric population – Workshop proceedings March 2012: Ensuring safe and effective medicines for an ageing population]. However, when considering extrapolation across drugs of two different MAHs (with different manufacturing processes, etc) and across different disease states, sometimes looking to both at the same time, the complexity of the exercise and the risks involved can increase substantially. As such, it</p>	<p>The paper will not discuss interpolation.</p> <p>This paper is about extrapolation. It will not deal with surrogate markers in depth.</p> <p>The role of extrapolation with respect to safety will be discussed, but the emphasis will be on the extrapolation of efficacy.</p> <p>Partly accepted. A number of different situations will be discussed in the paper, but it will not be possible to be completely comprehensive.</p>

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	<p>would be important in developing the reflection paper to also consider the implications of these more complex scenarios and situations where multiple types of extrapolation are being considered at the same time; thus clearly laying out expectations on what considerations go into extrapolation between diseases (e.g. disease-model), endpoints (e.g. comparator modelling), manufacturing processes (e.g. in silico approaches and IVIVC).</p> <p>3. It would be desirable not to be too prescriptive/restrictive so that flexibility and innovation with appropriate justification be possible. It should be mentioned that an algorithm for extrapolations could also entail modeling and simulation approaches (Reference is made to the recent EMA/EFPIA workshop on M&S: http://www.emea.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/07/event_detail_000440.jsp&mid=WC0b01ac058004d5c3). It is not feasible to predefine all specific model-based extrapolations. Nonetheless, expectations can be set with respect to points to consider and best practices.</p> <p>4. Interacting with the regulators: although a framework for extrapolation can be developed it is likely that the acceptability of extrapolation will mostly remain a case-by-case decision. In this respect, early interactions with the regulators should be stressed in the reflection paper and the process for scientific consultation and agreement on extrapolation clearly identified.</p> <p>5. Additional points that would need further consideration in the future reflection paper:</p> <ul style="list-style-type: none"> There is no statement on data quality. We would suggest addressing data 	<p>Accepted.</p> <p>Accepted.</p> <p>Accepted.</p>

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	<p>quality and the conditions of data collection.</p> <ul style="list-style-type: none"> • In addition, data sources could be defined. For instance is comparator modelling based on public domain data at study-arm level acceptable? This is typically nowadays used by the Industry in optimally designing trials. Can the same models be used for extrapolation resulting in label claims? And what is the expectation of data-collection quality? • It would be important to mention whether and how the forthcoming reflection paper will impact the therapeutic area specific guidelines or paediatric development guidelines, e.g. would the possibility of extrapolation be integrated into therapeutic area guidelines more than it currently is? Given the globalisation of drug development, more guidance around extrapolation of results from non-EU patients to the EU population would be helpful. 	
2	<p>We highly appreciate the publication of such a concept paper which encloses the aim of reducing the need to generate additional information (types of studies, design modifications, number of patients required) in order to reach conclusions for the target population. At this stage, we do not have much comment.</p> <p>However, the following guidelines that will be generated would need to be more specific. A key question is to establish whether available data are appropriate for complete (requiring only PK studies) or partial (requiring PK+PD studies) extrapolation strategy. This point should be clarified, preferably by providing some guidelines or rules.</p> <p>The use of “surrogate biomarkers” should be possibly considered in order to help in the choice of extrapolation strategy, in particular when no previous data is available. For example, how a positive study with a surrogate marker be considered to support such an extrapolation strategy and to</p>	<p>Partly accepted. The reflection paper will not necessarily encourage the use of biomarkers in post-marketing studies.</p>

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	<p>what extend?</p> <p>Toxicity and efficacy biomarkers that are relevant should be encouraged for extrapolation strategies for example in post marketing commitments.</p>	
3	<p>NICE would like to thank the EMA for the opportunity to respond to this concept paper on extrapolation of efficacy and safety in medicine development. NICE's comments will reflect the perspective of a health technology assessment organisation. NICE would welcome the opportunity to participate as an interested party in some of the discussions that will take place alongside this consultation process.</p> <p>We understand the need to avoid unnecessary studies but would like to stress the importance of prospective studies in the practice of evidence-based medicine, and how such studies are relied upon extensively by NICE's independent advisory bodies in the decision making process. NICE has handled appraisals where extrapolation of data from trials in adults to children was considered, and below we share our experiences with some of our outcomes.</p> <p>In the technology appraisal of 'immunosuppressive therapy for renal transplantation in children and adolescents' (NICE technology appraisal 99, April 2006). Only a small body of evidence on clinical effectiveness was identified from RCTs involving paediatric renal transplant recipients, and the Committee accepted evidence from adults as a proxy for efficacy and safety in children (for example, treatment with ciclosporin and a meta-analysis on the effectiveness of mycophenolate mofetil in adults).</p> <p>During this appraisal, NICE Committees were faced with the challenge of providing recommendations on the use of immunosuppressive regimens in children and adolescent populations with little or no evidence, despite pleas from consultees requesting NICE to provide special attention to these populations. The Appraisal</p>	Partly accepted. There will be opportunities to comment in writing on the reflection paper and on any subsequent guidance documents. NICE representatives will also be able to attend any workshop convened to discuss the reflection paper.

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	<p>Committee's conclusion on the children and adolescent population were based partly by extrapolating the results of RCTs in adults, to children, and partly on the basis of UK practice. We believe that any use of extrapolation should be considered with some confirmatory evidence in the target population.</p>	
4	<p>Extrapolation is a key issue in the development of new anticancer medicines for children with cancer because:</p> <ul style="list-style-type: none"> • there is a need to speed up drug development in children when more than 800 oncology drugs are in development in adults • most of the new anticancer agents are targeted agents, that come or should come along with biomarkers to help select patients who may benefit from them. In addition, part of them is expected to be used and active at their optimal biological dose rather than at their maximum tolerated (MTD), as opposed to cytotoxic chemotherapy that has been developed during the last 40 years in paediatric oncology. <p>While extrapolation was not relevant in paediatric oncology in the past, it becomes a key issue for the next 15 years.</p> <p>We see three main areas where extrapolation should be considered and validated in the field of new drug development for children and adolescents with cancer.</p> <p>1. Early dose finding studies in children</p> <p>Phase I trials are needed in children with cancer to define the optimal dose for further evaluation, to describe the pharmacokinetic behaviour of the drug and to identify the first signs of antitumor activity.</p> <p>For the last 20 years, phase I trials have searched the MTD through dose-escalation trials using a 3 by 3 design. The only information used from the development in adults was the final selected dose and the first dose level in children was set up at 80% of the MTD in adults. This was an international</p>	<p>Partly accepted. The reflection paper will discuss the particular circumstances of anti-cancer medicines.</p>

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	<p>consensus published in the Journal of Clinical Oncology in 1996 (First author: M Smith).</p> <p>Nowadays, the design of dose finding paediatric studies for targeted agents should use extrapolated information from adults such as the target optimal plasma level, the dose–response curve in terms of toxicity and efficacy, the use of biomarker(s) to monitor the activity of the drug, a PB PK model to better define the first dose. Innovative designs beyond the 3 by 3 should be used and validated.</p> <p>In some cases, early phase trials in adults should accrue patients younger than 18 years (in particular when selection of patients is based on tumor biomarkers and when there is a scientific rationale).</p> <p>In addition, from our experience in the last years, we believed that the type of medicine (in particular monoclonal antibody versus small molecule) should be taken into account and is likely to influence the design of the dose- finding studies in children and adolescents children.</p> <ul style="list-style-type: none"> ITCC strongly believes that better extrapolation from adults in children and innovative designs should be used in the early dose-finding studies in children and adolescents with cancer. <p>2. Extremely rare cancers in children</p> <p>Some frequent cancers in adults occur at an extremely rare frequency in the paediatric population, such as thyroid cancer, melanoma, chronic myeloid leukaemia and several adenocarcinomas (breast, colon,...).</p> <p>Innovative targeted agents are developed in these cancers in adults and some of them prove to be active, or even very active, and are eventually marketed.</p> <p>Thanks to the EU Paediatric Medicine Regulation, these agents need to have an approved paediatric investigation plan at the time the drug is filed for a marketing</p>	

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	<p>authorisation in adults.</p> <p>Children and adolescents with these extremely rare adult cancers must have access to these drugs which proved to be active in adults and sufficient information is required to provide a safe and effective use in the paediatric population.</p> <p>However, running a classical development in the paediatric population is extremely challenging considering the extreme rarity of the paediatric patients. This is even more challenging when several drugs are approved in the same indication in adults and must be addressed in children.</p> <ul style="list-style-type: none"> ITCC believes that extrapolation of efficacy data should be considered in these extremely rare cancers, as well as lowering the age below 18 for inclusion of paediatric patients in adult trials. <p>In addition, the mechanism of a drug (i.e. its target or targeted pathway) which is developed in an adult malignancy/indication may be relevant for paediatric malignancies which are different from the adult indication. For example, B-RAF mutation is present in melanoma but also in low grade astrocytoma, ganglioglioma and histiocytosis in children.</p> <ul style="list-style-type: none"> ITCC believes that a paediatric development based on the mechanism of action (and thus the tumour biology) allows generating information (dose, PK, safety) in a larger population of children than those having the adult malignancy, in parallel to extrapolation of efficacy data. <p>This situation of extremely rare cancers is different from that of rare cancers occurring in teenagers and young adults such as Ewing tumours, soft tissue sarcomas, Hodgkin and non-Hodgkin lymphomas.</p> <ul style="list-style-type: none"> ITCC believes that PIPs should accept efficacy clinical trials which are run both in teenagers and in young adults when the disease occurs in both 	

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	<p>populations.</p> <p>3. Below 2 years of age</p> <p>Cancer occurs in human from birth to old age. However, cancer is very rare in children under the age of 2 years. In addition, malignancies in toddlers proved to be sensitive to current therapies and may sometimes spontaneously regress (neuroblastoma).</p> <p>Thus, the number of children younger than 2 years of age who are eligible for a new agent (i.e. with a relapsed or refractory disease) is extremely low.</p> <p>However, this is during the first 24 months that the ontogenic changes (in particular in drug metabolism) are likely to impact drug disposition and the recommended safe dose.</p> <ul style="list-style-type: none"> ITCC believes that extrapolation should be used for the very young children in terms of drug efficacy and that the use of innovative methodology such as PBPK modelling should be further expanded to define the dose while using the data (including PK data) from the very few patients who may be treated under the age of 24 months. <p>4. Extrapolation of safety</p> <p>Acute and long-term safety of new anticancer drugs in children and adolescents with cancer needs to be adequately prospectively addressed. There are many specificities in the paediatric and adolescent population that may impact the type, the incidence, the severity and the consequences of acute and long-term side-effects.</p> <ul style="list-style-type: none"> ITCC believes that the level of extrapolation regarding safety, if any, should be very low and that long-term follow up of children exposed to new anticancer drugs will be best implemented through programs set-up 	

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	<p>by or in collaboration with the paediatric oncology community.</p> <p>In summary ITCC supports the principles of the concept paper.</p> <p>We suggest that the proposed solutions are tested and explored in the field of paediatric oncology in order to validate their use with regard to the three main topics we identified and/or to identify the need of specific solutions.</p> <p>ITCC and its methodologists and pharmacologists which are deeply involved in innovative and new designs for drug development are keen to contribute to further development of a reflection paper.</p>	
5	<p>We suggest that the committee consider broadening their definition of extrapolation to include extrapolation beyond a placebo-controlled period, when there are ethical challenges with running a longer placebo-controlled trial. While this is a challenging task, there are times when a rescue arm must be put in place in a trial for ethical reasons and yet a later time point is of interest to evaluate the effect of the drug. This guidance could provide structure for the most appropriate way to handle this challenge.</p>	Not accepted. This is outside the scope of the paper.
6	<p>EVM welcomes the opportunity to participate in the consultation of the Concept Paper on Extrapolation of Efficacy and Safety in Medicines Development and acknowledges that there is a need to develop a framework for extrapolation approaches. Furthermore, EVM believes that vaccines (prophylactic and therapeutic vaccines) should be included in the scope of this reflection.</p> <p>There are numerous examples where extrapolation of efficacy and safety data has played a critical role in the development of new vaccines.</p> <p>Indeed, demonstration of efficacy is not always feasible in all age groups (e.g. because of a low disease incidence in some age groups), in all populations (e.g. in subjects with specific medical conditions) or for all vaccine components (e.g. rare</p>	Partly accepted. The reflection paper will set out a number of broad principles to be considered and/or applied when considering the use of extrapolation and the supportive data required in the population to which, for example efficacy, will be extrapolated. Detailed guidance on extrapolation with respect to vaccine development is best handled in vaccine specific guidance to ensure coherence with the body of guidance on vaccine development.

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	<p>strains of the targeted pathogen). In addition, when placebo-controlled efficacy trials are not ethically acceptable because another vaccine targeting the same condition is already approved, licensure of new products is based extrapolation approaches.</p> <p>Situations where extrapolation of data is performed for vaccines include but are not limited to the following examples:</p> <ul style="list-style-type: none"> • Immunobridging to extend indication of the same product: <ul style="list-style-type: none"> – To another age group – To another medical condition – From one region/country to another • Immunobridging to extrapolate data: <ul style="list-style-type: none"> – From one product to another generation of the product [e.g. change manufacturing process, inclusion of additional antigens (e.g. Prevenar 13)] – From one product to a product of the same class (e.g. pneumococcal vaccines, meningococcal vaccines, flu vaccines, etc.) • Persistence of efficacy is extrapolated from immunogenicity at early time points, persistence of the immune response and statistical modelling • Extrapolation of efficacy can be based on surrogate endpoints (e.g. use of persistent infection instead of histopathological endpoint as surrogate maker of efficacy against cervical cancer for rare HPV types) • Extrapolation of safety: <ul style="list-style-type: none"> – By performing meta-analyses (e.g. for adjuvanted vaccines) 	

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	<ul style="list-style-type: none"> – After removal/reduction of a vaccine component (e.g. removal of thiomersal) – To change the vaccination schedule (e.g. safety of a 3-dose vaccination schedule extrapolated to a 2-dose vaccination schedule) <p>Should vaccines be in the scope of the future Reflection Paper on extrapolation of efficacy and safety in medicines development, vaccine specificities should be properly addressed when discussing the development of an extrapolation concept, such as:</p> <ul style="list-style-type: none"> • For prophylactic vaccines, the extrapolation concept should take into account similarity of epidemiology rather than similarity of disease as currently mentioned in the document • For vaccines, similarity of medicine disposition and effect is not based on PK/PD but on the immune response (immuno data or correlates of protection (COP)). This concept applies to both prophylactic and therapeutic vaccines and therefore there is need to discuss on the correlates of protection and how immuno data will be used. • The concept of different extrapolation categories needs to be clearly defined and needs to be adapted to vaccine specificities. <p>Finally, the EVM would like to comment that formalisation of the concept paper is interesting and could be beneficial, but nevertheless care has to be taken to allow its application to a broad range of different medicines and situations (worldwide developments) without resulting in EU- specific 'constraints'.</p>	
7	The concept paper aims to cover the principles and rationale for extrapolation in general and does not intend to deal with special cases of extrapolation. Although, in case of the development of similar biological medicinal products (i.e. biosimilars)	Partly accepted. The reflection paper will set out a number of broad principles to be considered and/or applied when considering the use of extrapolation and the

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	<p>extrapolation of clinical efficacy and safety data to other indications of the reference medicinal product is an inherent part of the clinical developments and biosimilar approvals, the underlying concept is completely missing from the discussion in this Concept Paper.</p> <p>Biosimilar medicinal products are representing a special category of candidate medicinal products for which the concept of extrapolation should also apply under certain circumstances discussed in the relevant biosimilar guidelines. In case of biosimilars, comparative assessment of quality, non-clinical, and clinical data obtained with the test and reference products is needed and high degree of similarity at all levels has to be demonstrated. The information gained from the previously mentioned comprehensive comparability exercise together with the overall knowledge about the originator reference product provides the basis for extrapolation. As such the comparability exercise forms the basis for biosimilar developments and the applicability of extrapolation principles together with its validation require a different approach from the one applied for other medicinal products in general.</p> <p>Criteria for extrapolation of clinical efficacy and safety data for biosimilar medicinal products to other indications approved for the reference medicinal product are also discussed in multiple product and product class specific guidelines concerning biosimilars. The general principle is that high degree of similarity at all levels including structural, functional, pharmacokinetic and pharmacodynamic properties has to be established first, then the demonstration of the clinical comparability in one indication will allow the extrapolation of the results to the other indications of the reference medicinal product if the mechanism of action and/or the receptor or the target of the product are known to be the same.</p> <p>Therefore the EGA kindly ask EMA to seek the review and agreement on the</p>	<p>supportive data required in the population to which, for example efficacy, will be extrapolated. Detailed guidance on extrapolation with respect to biosimilar products is best handled in specific guidance to ensure coherence with the body of guidance on the development of biosimilar medicinal products. The biosimilar medicinal products working party will be consulted in order to ensure that the reflection paper is compatible with guidance on biosimilar medicinal products.</p>

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	concept paper by the Biosimilar Medicinal Products Working Party besides the listed working parties that are already involved in the consultation.	
8	We welcome this opportunity to comment on the recently published document EMA/129698/2012 (Concept paper on extrapolation of efficacy and safety in medicine development). We agree that there is both a need and possibility for a principled framework to guide the use of extrapolation in supporting medicine development. Furthermore, we believe that a guidance document on this issue would be timely. While we largely agree with the objectives and content of the concept paper, we feel that there is a need to clarify some points within the document.	Accepted.
9	<p>General:</p> <p>We welcome the proposal by the EMA to produce a reflection paper, collate case studies and produce a subsequent guidance document on this topic.</p> <p>We fully support the need for “a framework for extrapolation approaches that are considered scientifically valid and reliable to support medicines authorisation.”</p> <p>The concept paper has a clear intent.</p> <ul style="list-style-type: none"> • The concept paper and proposed reflection paper and guidance could give more emphasis to the rigour required to assess evidence in the ‘source’ and ‘target’ populations, as only once fully delineated can it be clear where the gaps in evidence lie and whether evidence needs to be extrapolated (different target vs. source population) or applied (target has been included within source population). • The concept paper gives no indication that the planned work will build on major advances over the last 20 years in methodology to support evaluations of primary studies, systematic reviews, meta-analyses for direct and indirect comparisons, and in more complex evidence syntheses. 	Partly accepted. See below.

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	<p>Recent application of this work to reporting guidance for studies would be highly relevant to applicant submissions to the EMA (see Equator website http://www.equator-network.org/).</p> <ul style="list-style-type: none"> • The reflection paper could explore the need for clarity about the inevitable role of value judgements (particularly values about outcomes) in decisions about the applicability of evidence to source and target populations. This could help to make decision making more transparent and, by separating the assessment of evidence from values, make clearer the need for more research. • Extrapolation for medicines development defines a broad area of research and regulation that goes far beyond a 12 month schedule and needs substantial development. Rather than setting the goal of a reflection paper, checklists and algorithms as endpoints, these outputs should be seen as contributing to the longer-term development of more robust and transparent approaches. We propose that the reflection paper focuses on how EMA can develop an on-going research agenda on extrapolation with the academic community. • Much can be learned and built on from the systematic assessment of past EMA decisions on extrapolation. The proposed database of case examples (section 4) is to be welcomed, but this will be illustrative and highly selected. Much more could be learned from systematic and independent assessments of resources such as past PIP submissions. Such assessments should be opened up to a range of independent academic investigators, working with the EMA, to allow evaluation of past decisions and testing of alternative approaches across the full range of potential decisions. • We believe the Concept Paper has many overlaps with the recent EMA/EFPIA Modelling and simulation workshop (November 2011) where 	<p>The focus of the reflection paper will be to establish a framework for extrapolation.</p> <p>The contents of the PIPs are classified as commercially confidential and, as such, are not available to 3rd parties.</p>

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	<p>extrapolation using modelling and simulation was an underlying aspect of case studies, presentations and discussion.</p> <ul style="list-style-type: none"> • In particular, break out session 3 was focused on “M&S as a tool to bridge efficacy and safety data in some special populations”. The discussions and output from this session, in particular, should be considered in development of the reflection paper and subsequent guidance documents. • A key point in this field is the importance of a model driven approach to quantify risk-benefit based on the available data and its use in extrapolating to different situations. The reflection paper and guidance documents should clearly state that the ‘gold standard’ for extrapolation is the development of integrated physiologically and pharmacologically based mathematical models of PK-PD and disease progression. • It is clear that extrapolation for efficacy and safety will have different requirements. Extrapolation in terms of efficacy can often be done with a greater degree of confidence and less risk. While it is clear that greater caution is to be expected when considering extrapolation based for safety. The reflection paper and subsequent guidance document should give some separate consideration to extrapolation for efficacy and safety. • The terms “validation” and “confirmation” in section 3D/3B do seem to be at odds the concept of “partial extrapolation” and “full extrapolation”(EB) where a reduced development programs will be undertaken and more limited additional data assembled. Would the term “evaluation” be more in line with the concept that sufficient evidence has to be attained in order to “qualify” the extrapolation. <p>Scope:</p> <p>We welcome the recognition of “several gaps in knowledge that need to be</p>	

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	<p>resolved". The report flags important gaps in knowledge, many of which are major areas of scientific endeavour. However, the focus on developing algorithms for extrapolation and (in section 3b-quantitative evidence) on quantitative synthesis of all existing data lacks emphasis on the importance of exploring the risk of bias and uncertainty around the evidence contributing to each step of the causal pathway – the building blocks of any model.</p> <ul style="list-style-type: none"> • It is stated that extrapolation can be generally defined as inferences in a subgroup that has not been studied, or in a condition or product that has not been studied directly. However, it is not clear whether this also includes extrapolation with respect to duration of therapy or dose. Can the scope be clarified? • Similarly, it is not clear what is covered by the term "conditions". Does this only cover different disease stages, or different indications, maintenance vs. acute treatment etc or does it also extend to controllable conditions such as fasted vs. Fed states and change to/addition of background medication? 	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>modelling to estimate the health benefits over an extended time horizon (that is, beyond the trial period). Importantly, we extrapolate <i>within</i> the same target population and consider both clinical and biological plausibility of the inferred outcome (NICE Methods Guide, June 2008).</p> <p>In applying data from one group of patients to estimate effects in another, NICE prefers the term 'generalisability' or 'external validity' (see CONSORT statement).</p> <p>Proposed change (if any):</p> <p>Suggest consideration be given to an explicit definition to EMA's use of the word 'extrapolation' and acknowledgement that an alternative definition is used in health technology assessment.</p>	
Page 2/7 1 st paragraph (Lines 12 - 17)	1,6	<p>Comment:</p> <p>The introduction makes reference to types of extrapolation and includes as an example, extrapolation with related medicinal products. This suggests that there might be opportunity to extrapolate the use of a medicine in combination with a marketed product to the use with other marketed products in that class (aka Comparator modelling). If this was intended, this should be clearly stated in future guidance documents, e.g. in the database of case examples.</p> <p>Comment:</p> <p>Related conditions could be based on several aspects, e.g. similar aetiology, mechanism of action, treatment options. It is</p>	Partly accepted. The wording of the concept paper will not be amended, but the principles outlined in the comments will be taken forward in the reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>suggested to clarify the basis for selecting related conditions or mention these different aspects.</p> <p>Comment:</p> <p>In addition, some changes are proposed to keep consistency in the wording and also clarify it and for further consideration in the forthcoming reflection paper.</p> <p>Proposed change (if any):</p> <p>... from studies in one or more subgroups of the patient population (source population), or in related condition or with related medicinal products, to make inferences for another subgroup of the <u>patient</u> population (target population), or condition or <u>medicinal</u> product, thus reducing the need to generate additional information <u>through, for example, additional studies, study design modifications, or increased number of patients</u> (types of studies, design modifications, number of patients required) to reach conclusion...</p> <p>Comment:</p> <p>A single study may be able to demonstrate efficacy for selected populations, thus the number of studies should be considered when defining the additional information.</p>	
Page 2/7 2 nd	1	<p>Comment:</p> <p>It would be useful to state early on the reasons and</p>	Not accepted. The text of the concept paper will not be amended. In addition, we do not consider that the two suggested examples are relevant.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
paragraph (Lines 18 – 22)		<p>justifications for extrapolation. In many cases there are no alternative methods (such as in paediatrics or orphan indications) and extrapolation is necessary.</p> <p>Moreover, in addition to the two rationales for extrapolation that are given: to avoid unnecessary studies in the target population or in situations where the feasibility of studies is restricted, a 3rd one could also be considered: the need for clinical studies in new target populations.</p> <p>Proposed change (if any): The primary rationale for extrapolation is to avoid unnecessary studies in the target population for ethical reasons, <u>for unmet medical need</u>, for efficiency, and to allocate resources to areas where studies are most needed. Alternatively in situations where the feasibility of studies is restricted <u>or where clinical studies in new target populations are needed</u>, extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources.</p>	
Page 2/7 3 rd paragraph (Lines 23 – 27)	1	<p>Comment:</p> <p>The type of extrapolation considered for this potential guidance should be clarified, i.e. is it extrapolation of efficacy only? How acceptable is it to extrapolate safety? The reflection paper would likely need to differentiate between cases, especially in the case of safety where there could be variations of the population that could impact safety of the product, and similarly with extrapolation of efficacy or safety between different</p>	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>diseases.</p> <p>If the scope remains wide, the reflection paper should be structured in such a way to avoid strict requirements for a certain type of extrapolation in order not to complicate the process for simple cases.</p>	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
2. PROBLEM STATEMENT			
Page 2-3/7 (Line 34 – 65)	1,7	<p>Comment:</p> <p>The reflection paper should preclude any reference to extrapolation of safety/efficacy that is improbable (e.g. animals to humans or healthy volunteers to patients).</p> <p>Comment:</p> <p>This paragraph should be amended and rephrased in order to be applicable for special classes of medicinal products such as biosimilars. As such modelling and simulation should be applied only in the case of certain medicinal products, and the medicinal product's mechanism of action should be also taken into consideration.</p> <p>Comment:</p> <p>This paragraph should also be modified to become applicable for special situations where clinical data from the target indication(s) might not be available, e.g. in the case of biosimilar medicinal products.</p> <p>Comment:</p> <p>Clarification of the quantitative basis and models would be useful: what kind of models and what would be the basis for making the necessary assumptions to support an extrapolation concept? Should all model based approaches meet the requirements currently set for confirmatory evidence if the extrapolation is used for an approval? If so, how should these</p>	<p>Not accepted. There are already examples of extrapolation of efficacy from animals to humans eg in the development of medicinal products against agents of bioterrorism.</p> <p>The reflection paper will set out broad principles which are compatible with most situations. For special classes of product eg biosimilar products, the specific guidance documents will apply.</p> <p>Requests for clarification will be taken forward in the reflection paper.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>requirements be determined?</p> <p>Comment:</p> <p>The bullet point list misses the topic "Dealing with uncertainty and risk" from Section 3 as one element of the proposed framework. It is suggested to add the topic to the list for further consideration in the forthcoming reflection paper.</p>	
<p>Page 2/7</p> <p>1st bullet</p> <p>(Lines 40-43)</p>	1,6,7,9	<p>Comment:</p> <ul style="list-style-type: none"> • It is also important to take into account data collected beyond clinical studies -- in pharmacoepidemiology / drug utilization /registry studies, etc., giving insights into real life safety and effectiveness. • It is also important to show similarity of safety profile. • The modelling and simulation approach cannot be used for hypothesis testing, but it can be planned in advance for making a quantitative decision. We would suggest changing "explicit (quantitative) hypothesis" to "explicit exploration goal", to avoid the word "hypothesis". <p>Comment:</p> <p>Instead of mentioning modelling and simulation, it would be better to have a more general view. Moreover, references to knowledge gaps and issues that need to be resolved should include the influence of patient factors on disease (progression) which may in some cases have a larger impact than exposure of the investigated drug.</p> <p>Proposed change (if any):</p>	<p>Partly accepted. Safety will be handled separately as extrapolation, if any, of safety is very different. The reflection paper will not deal with vaccines in detail. The reflection paper will take a pragmatic approach in its discussion of quantitative data.</p> <p>We are not amending the concept paper, but we will take forward accepted principles in the reflection paper.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>change " ... and include the use of modelling and simulation approaches" with " ... and include the use of mathematical and statistical approaches".</p> <p>Comment:</p> <p><i>"systematic synthesis of available data (in vitro, preclinical, clinical)"</i></p> <p>Epidemiological data in the field of Vaccines Development could also be very helpful. These data would include case control studies or observational studies which could provide supportive evidence of efficacy in low incidence diseases (e.g. Hepatitis B in neonates)</p> <p><i>"... to develop and explicit (quantitative) hypothesis regarding the similarity of the disease..."</i></p> <p>The development of an explicit plan is indeed useful but it should be taken into account that sometimes the quantitative data cannot be provided.</p> <p>Comment:</p> <p>Development of an extrapolation concept: this would build on a systematic synthesis of available data (quality, in vitro, preclinical, clinical), thorough scientific arguments to justify similar mechanism of action in the case of different indications and in certain cases include the use of modelling and simulation approaches, to develop an explicit (quantitative) hypothesis regarding the similarity of the disease and the similarity of response to intervention between source</p>	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and target populations.	
Page 2/7 2 nd bullet (Lines 44 - 45)	6,7	<p>Comment:</p> <p>This bullet point mentions a reduced set of supportive studies. EVM members wonder whether this concept paper is considering only a priori extrapolation plans where studies should be designed to fit into a plan.</p> <p>Alternatively the EMA could consider post hoc plan where a claim might be sought based on work already accomplished and a completed set of data that were not collected with an extrapolation in mind.</p> <p>Comment:</p> <p>In the special case of biosimilar medicinal products the extrapolation plan could be comprised solely of scientific justification based on a comprehensive data package gained from a quality, non-clinical and clinical comparability exercise and the overall knowledge about the originator medicinal product. Accordingly, in certain cases clinical data are generated in the most relevant and sensitive patient population and indication and no clinical data are needed in the target population.</p> <p>Proposed change (if any):</p> <p>Scientific justification of the extrapolation plan, proposing a reduced set of supportive studies in the target population when needed in accordance with the extrapolation concept.</p>	Partly accepted. The reflection paper will not deal specifically with biosimilar products. The concept paper will not be amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 2/7 3 rd bullet (Lines 46 - 48)	6,7	<p>Comment:</p> <p>The EMA should clarify which data is considered as “emerging data” and what is meant by “validation of the extrapolation concept”</p> <p>Comment:</p> <p>In this section the possibility of missing clinical data in the target indication(s) should be reconsidered in certain cases, i.e. especially for biosimilar medicinal products.</p> <p>Proposed change (if any):</p> <p>Validation of the extrapolation concept by relevant emerging data (clinical data in the target population, if applicable, as well as quality, in vitro, preclinical, or other population data); or, if the concept cannot be validated, update of the extrapolation concept and plan.</p>	Request for clarification accepted. We are not amending the concept paper.
Page 2/7 4 th bullet (Lines 49 - 50)	7	<p>Proposed change (if any):</p> <p>Interpretation of the limited data in the target population in the context of information extrapolated from the source population(s). When clinical data is not available from the target population(s), based on the comprehensive evaluation of all available data, appropriate scientific justification needs to be provided to support the extrapolation on a case-by-case basis.</p>	Not accepted. We are not amending the concept paper. We will consider taking the principle forward in the reflection paper.
Page 3/7 Apply to the	1,6,7	<p>Comment:</p> <p>The current limitations of extrapolation are recognised and</p>	Partly accepted. There are constraints of length that will limit the expansion of any section of the reflection paper. Specific challenges in different therapeutic areas may be best handled

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
list of bullet points (Lines 51 - 65)		<p>accepted. However, in this fast moving area of science, terminology recognising that increasing knowledge could shape future acceptability should be added.</p> <p>Comment:</p> <p>We would suggest to expand this section in the future reflection paper:</p> <ul style="list-style-type: none"> to consider challenges and limitation in level of extrapolation potential in different therapeutic areas. <p>(This consideration will link with the to be collated "database of examples from various therapeutic areas" stated in Section 4)</p> <p>Comment:</p> <ul style="list-style-type: none"> When discussing gaps consideration about risk management in the extrapolated population should be added. This goes hand-in-hand with quantifying the uncertainty of the extrapolation --- how do we manage this uncertainty. Another important consideration in the extrapolation is to define the treatment paradigm that this is falling into – maybe it is a second line therapy as opposed to first line (i.e., treatment history). <p>Comment:</p> <p>A database of case examples from various therapeutic areas is being planned by the Agency. It would be helpful to have all elements of extrapolation framework development covered for</p>	through therapeutic area-specific guidelines. In addition, we are not amending the concept paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>such examples to illustrate how the knowledge gaps are addressed.</p> <p>Comment:</p> <p>The 6 last bullet points are unclear and should be further clarified. Moreover, there is a repetition between 'how validating the assumption in the extrapolation concept' and 'how dealing with uncertainty and risk'.</p> <p>Comment:</p> <p>The similarity of the medicinal product's mechanism of action between indications should be considered in this section. A separate sentence should be added to the list</p> <p>Proposed change (if any):</p> <p>addition to the list:</p> <p>how defining and quantifying similarity/sameness of mechanism of action between indications</p>	
Page 3/7 2 nd bullet (Lines 54 – 55)	1	<p>Comment:</p> <p>Feasibility is particularly important for certain populations with uncommon diseases. Rare diseases would need special consideration (reference is made to the Guideline for clinical trials in small populations)</p>	Accepted.
Page 3/7 3 rd bullet (Lines 56 –	1,6	<p>Comment:</p> <p>It would be important to clarify whether relevant emerging data include data from sources other than studies supported by the</p>	Partly accepted. We are not amending the concept paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
57)		<p>MAH?</p> <p>Comment:</p> <p>The terminology "other population data" is restrictive as it implicitly relates to the primary use of paediatric examples.</p> <p>In addition the sentence "if the concept cannot be validated, update of the extrapolation concept and plan" is not clear.</p> <p>A rewording is thus proposed.</p> <p>Proposed change (if any):</p> <p>Validation of the extrapolation concept by relevant emerging data (clinical data in the target population, as well as in vitro, preclinical, or other population data <u>in similar class of drugs</u>); or, if the concept cannot be validated, update of the extrapolation concept and plan <u>should be modified to enable validation</u>".</p> <p>Comment:</p> <p>It would be important to take into consideration the natural history of the new indication for extrapolation since it may take some time to show efficacy or detect safety issues.</p> <p>There is also a need to consider validity of historical data (links to bullet point 8).</p> <p>How to define the similarity of risk factors of the population and underlying baseline characteristics</p> <p>Comment:</p>	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Defining and quantifying similarity of disease applies also for disease prevention and not only for disease progression.	
Page 3/7 4 th bullet (Lines 58 – 59)	1	Comment: We would recommend that consideration should be given to the amount of previous data on an individual basis, taking into account the safety of the product, AE profile, disease type and overall risk/potential risk in the extrapolated disease.	Partly accepted. Safety will be handled separately from efficacy.
Page 3/7 5 th bullet (Line 60)	1	Comment: Any anterior published, peer reviewed information need to be consistent, recognised and sound if it is going to be used to support the extrapolation approach. Proposed change (if any): We would suggest expanding the sub-bullet point on “how weighing the strength of prior information” to include the complexity that might be encountered in power assessment of sampling size using prior information and difficulties in bridging multi-sources of information. This can link to sub-bullet point “how dealing with uncertainty and risk”	Principle accepted and will be taken forward in reflection paper. We are not amending the concept paper.
Page 3/7 9 th bullet (Line 64)	1	Comment: One way of dealing with uncertainty and risk is to consider addressing the following questions: <ul style="list-style-type: none"> • What is the current population and presuming clinically meaningful effect, is it safe? • What is the clinical need - if there are effective 	Some principles accepted and will be taken forward in reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>treatments then why extrapolate?</p> <ul style="list-style-type: none"> • What are the concurrently used meds and will these influence the efficacy and safety of the product in the new indication? • Is the risk benefit justified in the extrapolated population? • Can sufficient measures be put in place to monitor safety and efficacy in the new population? 	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
3. DISCUSSION			
Page 3/7 1 st paragraph (Lines 74-75)	1	Comment: The last sentence "Safety studies are considered always necessary as safety profiles may differ from those in adults". This is true, but it is the first place where the importance of safety and the fact that it most likely cannot be directly extrapolated is mentioned. This point should receive more attention and emphasis. The apparent "restriction" of such statement to differences between adults and children is not clear since the concern is present for all areas of extrapolation.	Accepted.
Page 3/7 (Line 70)	1	Comment: With reference to the statement: <i>"if the exposure-response relationship of the medicinal product is assumed to be similar"</i> . It would be valuable to have some guidance on what criteria are expected to be met. Historically, a solid argument on the aetiology of the disease has been considered adequate; however there are recent examples where this has not been accepted.	Accepted.
Page 3/7 2 nd paragraph (Lines 76-78)	7	Comment: Criteria for extrapolation of clinical efficacy and safety data for biosimilar medicinal products to other indications approved for the reference medicinal product are also discussed in multiple product and product class specific guidelines concerning biosimilar medicinal products. The	Accepted in principle. The concept paper will not be amended. This will be taken forward in the reflection paper. There will not be detailed references to biosimilar products.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>general principle is that the demonstration of the clinical comparability in one indication will allow the extrapolation of the results to the other indications of the reference medicinal product if the mechanism of action and/or the receptor or the targets of the drug are known to be the same.</p> <p>Proposed change (if any):</p> <p>Similar principles are discussed in the EMA guidelines on the 'ICH E11 Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)' and 'Role of Pharmacokinetics in the development of medicinal products in the Paediatric Population (CHMP/EWP/147013/2004)' and in non-clinical and clinical guidelines on similar biological medicinal products.</p> <p>(e.g. EMEA/CHMP/BMWP/31329/2005, EMEA/CHMP/BMWP/102046/2006, EMA/CHMP/BMWP/403543/2010)'.</p>	
3. A: CLINICAL CONTEXT			
Page 3/7 (Lines 83-84)	1	<p>Comment:</p> <p>The examples provided of rationale for extrapolation appears to reflect on reasons why a study would otherwise be difficult to conduct. However it does not address cases where extrapolation would optimise clinical development, e.g. where both a surrogate endpoint/biological marker and clinical endpoint have been demonstrated in a source population and then further studies in a target population are proposed with</p>	Accepted in principle. The concept paper will not be amended. This will be taken forward in the reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>that surrogate/biological marker, with extrapolation to the clinical endpoint in the source population.</p> <p>Proposed change (if any):</p> <p>"Justification is needed why extrapolation is considered rather than a complete set of prospective studies (e.g. not to replicate studies for ethical and resource reasons, feasibility restrictions, <u>opportunity to optimise the clinical development programme</u>)"</p>	
Page 3/7 (Lines 84-86)	1	<p>Comment:</p> <p>"These situations..." It is not clear what situations are being referred to. Please expand and clarify in the forthcoming draft Reflection Paper.</p>	Accepted.
3. B: DEVELOPMENT OF AN EXTRAPOLATION CONCEPT			
Page 4/7 (Lines 88-116)	1, 3, 7	<p>Comment:</p> <p>Clarification of the quantitative basis and models would be useful: what kind of models and what would be the basis for making the necessary assumptions to support an extrapolation concept? Should all model based approaches meet the requirements currently set for confirmatory evidence if the extrapolation is used for an approval? If so, how should these requirements be determined?</p> <p>Comment:</p> <p>The similarity of the medicinal product's mechanism of action</p>	Partly accepted. Examples will be given.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>clinical efficacy and safety endpoints <u>and assessment tools</u></p> <p>Comment:</p> <p>In “B. Development of an extrapolation concept” of page 4, it starts with “Biological and pharmacological rationale” which consists of a list for similarity items to be assessed. These items will then be evaluated by “Quantitative evidence”. The relationship between the uncertainty/level of similarity and developing “Extrapolation concept” could be stated more explicitly. Especially, one of the critical questions of this paper is to decide what is the sufficient level of certainty in the relationship between the similarity items and quantitative evidence to justify the extrapolation.</p> <p>Comment:</p> <p>The subsection states: “Similarity of disease (subtypes based on aetiology, pathophysiology, clinical manifestation etc)”</p> <p>It is suggested to include genetic variation as part of the subtypes in the reflection paper.</p> <p>We would also recommend considering separating similarity of disease (symptoms and mechanism of disease) and similarity of disease progression (mechanism of disease progression and/or regression) especially in the therapeutic area related to immune system.</p>	<p>Accepted.</p> <p>Accepted</p>
Page 4/7 2 nd bullet	1	<p>Comment:</p> <p>The concept paper refers to “groups”. We would recommend that the reflection paper makes clear that subgroups of the</p>	<p>Accepted. (No further explanation necessary)</p> <p>Accepted.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<i>Disease progression</i> (Lines 98-99)		population are covered when referring to "groups".	
Page 4/7 2 nd bullet <i>PK and PD</i> (Lines 100-101)	1,6,9	<p>Comment:</p> <p>It is not clear why "age" should always be mentioned. It is just one of the possible covariates for extrapolation and as such not particularly informative as observed in the difference between the elderly and frail.</p> <p>Proposed change (if any):</p> <p>We would rather propose to indicate age as a potentially important co-variate:</p> <p>PK and PD: using existing data and physiology-based PK (and PD) modeling and simulation to investigate the relationship between PK/PD, age, and other important co-variates <u>(such as age, renal- and hepatic function, etc.)</u>.</p> <p>Comment:</p> <p>We would recommend adding "literature data" to support all existing data (in-vitro, preclinical and clinical).</p> <p>Comment:</p> <p>Assessment of patient factors influencing disease progression must be emphasized. Also the strength of the PKPD-relation must be defined.</p> <p>Proposed change (if any):</p>	<p>Partly accepted. The concept paper will not be amended. This will be taken forward in the reflection paper.</p> <p>Accepted</p> <p>Accepted</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>change “.. PK and PD: using existing data and physiology-based PK (and PD) modelling and simulation to investigate the relationship between PK/PD, age and other important covariates.” with “: “... PK and PD: using existing data and physiology-based PK (and PD) modelling and simulation to investigate the relationship between PK/PD, body size, maturation, age and other important covariates.”</p> <p>Comment:</p> <p>In Vaccines, we do not expect PK/PD correlation with the immune response. PD data (e.g. seroconversion criteria when the induction of humoral response with a specific antibody to a vaccine is correlated with efficacy) could be also considered as sufficient evidence for an extrapolation concept.</p> <p>Also, there is a reference to covariates to be used to facilitate the extrapolation. The relationship of the covariate to the response is often a function of the range of the covariate studies. It would therefore not be feasible to simply assume that the relationship remains constant in an unstudied area in order to validate an extrapolation to another variable.</p>	<p>Accepted in principle. The concept paper will not be amended. This will be taken forward in the reflection paper.</p> <p>Accepted.</p>
<p>Page 4/7</p> <p>2nd bullet</p> <p><i>Clinical response</i></p> <p>(Lines 102-104)</p>	1	<p>Proposed change (if any):</p> <p>“Clinical response: quantitative synthesis or modelling of all <u>relevant</u> existing data...”</p>	<p>Partly accepted in principle. The concept paper will not be amended. This will be taken forward in the reflection paper.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 4/7 3 rd bullet (Lines 106-110)	1,6,9	<p>Comment:</p> <p>The section on Extrapolation Concept appears directive and restrictive. Some changes are suggested.</p> <p>Proposed change (if any):</p> <p>Explicit specify hypothesis on the expected difference similarity in response to the medicine between the target population and the source population. All assumptions made and resulting uncertainties should be specified and the expected difference quantified to the greatest degree possible. The extrapolation will require expert interpretation and judgement to weight the existing evidence and fill in knowledge gaps.</p> <p>Proposed change (if any):</p> <p>Change bullet point "Full extrapolation: some supportive data to validate the extrapolation concept." with "Full extrapolation: limited supportive data in order to validate the extrapolation concept."</p> <p>Comment:</p> <p>The concept paper states that 'the extrapolation concept will require expert interpretation and judgement to weigh the existing evidence and fill in knowledge gaps'.</p> <p>Who will be providing the interpretation (EMA, the applicant or both)?</p>	Not accepted. The concept paper will not be amended. Any changes will be taken forward in the reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 4/7 3 rd bullet (Lines 111-116)	1	Comment: The document discusses the quality and robustness of the extrapolation and such concepts as “no extrapolation”, “partial extrapolation” and “complete extrapolation”. Although this is a concept paper some thought should be given as to how these are to be quantified in the future framework. Also defining the difference between extrapolation and interpolation in a dose-range should be useful to consider.	Partly accepted in principle. The concept paper will not be amended. This will be considered in the reflection paper.
Page 4/7 3 rd bullet <i>No extrapolation</i> (Line 113)	1	Comment: A rationale should not be needed for “No extrapolation”. Rationales should be needed when extrapolation would be chosen – either partial or full – but when a standard development with clinical studies being conducted is undertaken, the company should not have to justify conducting these studies; this should remain an internal company decision.	Accepted.
Page 4/7 3 rd bullet <i>Full extrapolation</i> (Line 116)	1	Comment: The last bullet in section mentions “some supportive data” to validate the extrapolation concept. The concept of “some supportive data” should be defined as the use of the word “some” suggests that partial extrapolation may need to be considered and, possibly, preferred to full extrapolation. In addition, perhaps some guidance could be provided in the future reflection paper in terms of what would be accepted, e.g. biomarker data (safety or efficacy?)	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
3. C: EXTRAPOLATION PLAN			
Page 4-5/7 (Lines 117-141)	1	<p>Comment:</p> <p>The current section “3C. Extrapolation Plan” is a collection of extrapolation concepts, in addition to those presented in Section 3B. It is recommended to refer to “planning” instead of “plan”, as a formal plan may not be a realistic approach, especially in early phase studies.</p> <p>Proposed change (if any):</p> <ol style="list-style-type: none"> 1. To incorporate the current content of Section 3C into that of Section 3B 2. To create a new Section 3C, called “3C. Extrapolation Planning and Reporting” with the following suggested content: <ul style="list-style-type: none"> • Extrapolation planning should start early in the development process, as it is driving the number and design of studies in the program (For PIP: already recommended at the time of Phase I). • In general, extrapolation planning may be a part of the clinical development planning documentation. In specific situations, it may be described in a dedicated document such as a PIP in paediatric extrapolation. Appropriate parts may then be included in other documents, such as briefing books for regulatory purposes, and in the methodology section of 	Not accepted. The concept paper will not be amended. The principles will be considered when drafting the reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>extrapolation reports.</p> <p>The reporting of extrapolation results should include a methodology section, covering all relevant aspects of extrapolation planning, the assumptions made (including relevant references and data sources), and the validation /verification strategy.</p>	Accepted.
<p>Page 4/7</p> <p>1st paragraph</p> <p>(Lines 118-123)</p>	1	<p>Comment:</p> <p>It may not be viable to use the data "generated" in the target population to validate the extrapolation, because the data "generated" in the target population are from the extrapolation. The validation should use the data "observed" in the target population.</p> <p>Comment:</p> <p><i>"the possibility to generate a set of rules and methodological tools for the reduction of data requirements (types of studies, design modifications, number of patients) in accordance with the degree of expected similarities should be investigated"</i></p> <p>There is a large variety of product types, conditions, populations, treatment approaches (new/old, environmental factors ...) that would make the reflection paper difficult to write and hard to follow. Flexibility should be left to the companies to design their extrapolation plans and tailor it to the specific case they are working on. Some requirements based on a rule may also not be available depending on the product, population etc. The "rules" mentioned in the concept paper should remain "suggestions", "best practices" or "points to consider". Also</p>	<p>Not accepted. Data generated in the target population support extrapolation. They are not from the extrapolation.</p> <p>Accepted.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		early dialogue would be considered useful.	
Page 5/7 2 nd paragraph (Lines 124-131)	1,7	<p>Comment:</p> <p>“Safety aspect” were considered in main text e.g. section 2, section 3, subsection B, D, E. However, in section 3 sub section C, safety aspect should have also been considered as principal scenarios.</p> <p>Proposed change (if any):</p> <p>We would suggest that the future reflection paper includes the following points:</p> <ul style="list-style-type: none"> • PK-safety aspect (extended to sub-bullet point 1) • Potential safety data available at target population to be supported by ‘Bayesian’ approach (extended to sub-bullet point 2) <p>Comment:</p> <p>A third “principal scenario” should be added for medicinal products where the absence of clinical data from the target population(s) could be justified like in the case of biosimilar medicinal products where the scientific basis of extrapolation is derived from the comprehensive comparative quality, non-clinical and clinical data (probably from a single relevant indication) and from the overall knowledge about the originator medicinal product including the mechanism of action in different indications.</p> <p>Proposed change (if any):</p>	Partly accepted. We are not amending the concept paper. The principles will be considered in the reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>addition of third scenario</p> <p>In specific cases, like in the case of biosimilar medicinal products, based on the available comparative quality, non-clinical data and based on the clinical data obtained in the source indication together with the overall knowledge about the originator medicinal product including the mechanism of action in different indications, limited or no clinical data from the target population(s) can be justified.</p>	
<p>Page 5/7</p> <p>2nd paragraph</p> <p>2nd bullet</p> <p>(Lines 128-131)</p>	1	<p>Comment:</p> <p>The 2nd scenario states “Some efficacy data are considered necessary in the target population the nature of which depending on the degree of extrapolation from the source population. Such a scenario could be supported by ‘Bayesian’ statistical approaches using prior information from the source population(s).” The proposed Bayesian approach can be extended to PK and PK/PD as well. Additional uncertainty/variability associated with bridge/extrapolation should be considered and incorporated. Alternatively, the two scenarios could represent two different types of information, and the Bayesian approach is a tool/methodology which is applicable to both.</p> <p>Comment:</p> <p>It would be useful to mention that an appropriate discounting of priors is often necessary. It is suggested to provide a brief explanation and add a relevant reference of such a Bayesian</p>	<p>Partly accepted. The concept paper will not be amended. The principles will be considered when drafting the reflection paper.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>approach (see <i>Jones et al. (2011; Clin Trials. 8:129-43).</i></p> <p>Proposed change (if any):</p> <p>Such a scenario could be supported by 'Bayesian' statistical approaches using prior information from the source population(s), <u>with appropriate discounting of the prior.</u></p> <p>Comment:</p> <p>Responder rates across a number of indications may be of value. There is a need to signify clinically relevant response in each case.</p>	
<p>Page 5/7</p> <p>3rd paragraph</p> <p>(Lines 132-141)</p>	1,6	<p>Comment:</p> <p>Statistical Perspectives</p> <p>The concept paper contains the general framework for extrapolation approaches to support medicine authorization. However, the application of extrapolation depends upon the purpose of extrapolation, the limitation of information, and biological rationale. The concept paper lists 5 plausible areas of extrapolation application examples and none of these areas have very distinguishing modelling assumptions, scientific background, and modelling approaches. The concept paper cites all examples based on pediatric studies (ICH E11). This may show the difficulty within other less defined areas lacking good examples. For instance on "from animal studies to humans", will regulatory agency allow for TQT studies waived when there is no QTc prolongation concerned in in-vivo studies? Or no matter what evidence supports the extrapolation, TQT</p>	<p>Not accepted. The reflection paper will set out general principles and will not aim to answer all specific questions.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>must be performed? Or the extrapolation can only be applied when TQT for certain drugs cannot be used on healthy volunteers? These questions have to be very specifically defined in the forthcoming reflection paper.</p> <p>Comment:</p> <p>The document uses paediatric extrapolation as an example to guide the reader. However there are examples in the document in which terminology related to age dependent extrapolation is used when it would be more pertinent to use less restrictive terminology to allow extrapolation in other situations.</p> <p>It would be helpful if the Agency could provide examples of approaches to extrapolation that haven't been used in paediatric investigation plans.</p> <p>Comment:</p> <p>The concept paper provides only paediatric examples. As the document deals with all various types of extrapolation, it could be useful to add different examples of extrapolation other than paediatrics ones.</p>	<p>Accepted</p> <p>Accepted.</p>
<p>Page 5/7</p> <p>3rd paragraph</p> <p>2nd bullet</p> <p>(Line 135)</p>	1	<p>Comment:</p> <p>It would be useful to be more explicit and explain the nature of extrapolation.</p> <p>Proposed change (if any):</p> <p>Dose-ranging or dose-titration studies, <u>with extrapolation to</u></p>	Partly accepted. The concept paper will not be amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<u>efficacy and/or safety of the selected dose."</u>	
Page 5/7 3 rd paragraph 4 th bullet (Line 137)	1	Comment: The use of terminology such as arbitrary renders the statement vague and is not helpful. Please clarify in the forthcoming reflection paper. Proposed change (if any): "Controlled study but arbitrary sample size; <u>i.e. the study is inadequately powered on its own.</u> "	Partly accepted. The concept paper will not be amended. This will be considered when drafting the reflection paper.
Page 5/7 3 rd paragraph 6 th bullet (Line 139)	1	Comment: Examples and guidance as to the acceptability of surrogate endpoints would be useful (perhaps with reference to appropriate other guidance). However surrogates can change as scientific/technical and clinical knowledge progresses, so dialogue is critical.	Partly accepted. The use of surrogate markers merits a separate paper. Any reference to surrogate markers will be in a general context only.
3. D: VALIDATION			
Page 5/7 (Lines 142-153)	1,7,9	General Comments: We recommend replacing the word "validation" by "verification", since "validation" is used in many contexts with different meanings. For the purpose of the concept paper, the methodology is based on assumptions that need to be "verified" rather than "validated". "Verification" alludes to observing independent data for its match with the predictions. In addition model "qualification" is often used to describe the process of evaluating the appropriateness of the model assumptions for its	Partly accepted. It may not be possible to quantify data requirements.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>purpose of predicting: i.e. are the data and model complexity scientifically robust enough for the intended extrapolation.</p> <p>However, it would be useful to mention that not all assumptions can be verified e.g. in instances where it would be unethical to gather the necessary clinical trial data in the target population, or when the target population is too small to carry out an appropriate trial.</p> <p>A verification and qualification strategy should therefore clearly state the assumptions which will be verified and those which will not, the reasons for not verifying them, the procedure(s) to perform the verification, and the timing (e.g. as a Phase IV commitment).</p> <p>In other words, how much data should be gathered to verify the extrapolated prediction? What should be the expected level of confidence (qualifying the model) in relation to a given prediction? For example, demonstrating equivalence of predictions and future observations may require an increased number of patients, should similar standards be implemented as for pharmacokinetic bioequivalence testing, especially in view of the large variability of many clinical endpoints.</p> <p>Comment:</p> <p>It would be helpful to define what constitutes “emerging data” in the Reflection Paper.</p> <p>Comment:</p> <p>It would be useful to provide guidance and examples on how</p>	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>much data need to be generated in the target population for the purpose of validation, and how much data can be considered enough to meet the purpose of verification?</p> <p>Comment:</p> <p>Clarification of the quantitative basis and models would be useful: what kind of models and what would be the basis for making the necessary assumptions to support an extrapolation concept? Should all model based approaches meet the requirements currently set for confirmatory evidence if the extrapolation is used for an approval? If so, how should these requirements be determined?</p> <p>Comment:</p> <p>If model assumptions and predictions can be validated by emerging data in the target population, the extrapolation will not be needed. It is suggested to reword the sentence for better clarity in the forthcoming reflection paper.</p> <p>Proposed change (if any):</p> <p>The emerging data in the target population shall be used for extrapolating into the target population to validate the extrapolation concept (model check".</p> <p>Comment:</p> <p>We generally think that the word "test" is a better choice than "confirm". Furthermore, if validation of extrapolation fails repeatedly, it should be mentioned that the extrapolation</p>	<p>Partly accepted. It may not be possible to fully quantify data requirements.</p> <p>Partly accepted. Some clarification will be given.</p> <p>Not accepted. Validation of the model assumptions and predictions does not mean that extrapolation is not needed. It means that the extrapolation approach is acceptable.</p> <p>Partly accepted. If validation of extrapolation fails repeatedly then it will not be possible to extrapolate at all.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>concept needs to be changed to “No extrapolation”.</p> <p>Comment:</p> <p>The validation process should be in line with the type of “principal scenario” which is applied for the particular medicinal product. Therefore in such cases where limited or no clinical data from the target population(s) can be justified (e.g. biosimilar products) instead of the validation during the evaluation, the focus should be on the totality of evidence.</p> <p>Proposed change (if any):</p> <p>A separate paragraph should be added to this section</p> <p>In case of biosimilar medicinal product development, the comprehensive comparability exercise between the originator and the biosimilar medicinal product on quality, non-clinical and clinical level should be able to support the similar clinical efficacy and safety of the two medicinal products. Consequently, such comparability data together with the thorough evaluation of the sameness of the mechanism of action in the source and target indications can provide appropriate scientific justification for the extrapolation.</p>	<p>Partly accepted. Any extrapolation process involves looking at the totality of the evidence.</p> <p>Not accepted. The concept paper will not be amended. This principle will be considered when drafting the reflection paper.</p>
Page 5/7 (Lines 150-152)	1	<p>Comment:</p> <p>In the concept paper, it is stated: “the need to generate more data in the target population should be assessed and the extrapolation plan adjusted”. However, all data generated are using information from the source data, to generate more data</p>	Not accepted. If data do not confirm that it is possible to extrapolate then it may be that no extrapolation is possible.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>in the target population will not add any new information nor correct false information. If the data do not confirm the extrapolation, the most important thing is to check the true extent of similarity and extrapolation method/model. Then more attention should be paid to the information included in the source, whether to include more information (data) to the source population, or exclude inaccurate information (data) and information with too much potential measurement errors.</p> <p>Comment:</p> <p>In the section on extrapolation validation it is stated that if the clinical data does not confirm the extrapolation, the model should be updated and validated again with further data. The section talks about adaptive designs but this may also imply further trials would have to be run in the event of an extrapolation failure. These further trials are only required in this case and so how should these further trials be presented in the PIP in a way a sponsor is not committed to them if the initial extrapolation succeeds? Comprehensive predefinition will be very challenging. The process of qualification and verification on the other hand could be considered for the PIP.</p>	<p>Not accepted. The reflection paper will apply to extrapolation of efficacy in general and will not address specific problems in relation to Paediatric Investigation Plans.</p>
3. E: EXTRAPOLATION			
<p>Page 5/7</p> <p>(Lines 154-157)</p>	1	<p>Comment:</p> <p>This statement is unclear. It would be helpful to clarify what is meant by target and source population?</p> <p>Please provide guidance/examples on what would be considered</p>	<p>Accepted.</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<p>evaluations to investigate the operating characteristics of a selected method. This is an important step when selecting an appropriate method for the extrapolation plan.</p> <p>In addition, this section could also discuss limitations of the safety assessment caused by e.g. less exposure than usually required according to ICH E3 or patient groups not yet treated with the drug and what is needed to fill the gaps (e.g. Post-Authorization Safety Study).</p> <p>Proposed change (if any):</p> <p>Add two new bullet points to the existing list:</p> <p>Whenever possible, quantify potential errors rates and investigate the operating characteristics for given approaches in the context of a prior belief.</p> <p>Missing or limited information (e.g. limitation of safety data due to limited exposure, untreated patient groups) and follow-up activities (e.g. need of a post-authorization safety study)</p> <p>Comment :</p> <p>In case of there are no data in the target population and a “full extrapolation” plan is considered, it will be very difficult to determine reasonable estimates of uncertainty.</p> <p>In case a “partial extrapolation” plan is considered, clear guidance should be provided on what is acceptable for emerging data and the prior data to determine estimates of uncertainty.</p>	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 6/7 4 th bullet (Line 169)	1	<p>Comment:</p> <p>Does this bullet point include non-linear mixed effect analyses of pooled data? This is regularly done for population PK and more often now for population PK/PD data. Could, for example, a population analysis of dose-response or dose-concentration-time-response provide the necessary information to derive a dosage regimen adequate for an entire treatment population (at least for efficacy), if it was prospectively planned for a series of (future) clinical studies covering a pre-specified range of patient characteristics? What is the role of meta-analytical approaches based on a package of clinical trials, given that often two or more independent confirmatory trials are conducted? In addition to meta-analysis of the clinical trials of an investigational compound the supportive evidence role of comparator modelling using literature-based/public domain data could be indicated.</p> <p>Proposed change (if any):</p> <p>“Prospectively planned meta-analysis, including future trials, to account for uncertainty.” Besides clinical trials of the investigational compound supportive evidence can be obtained from other existing drugs with similar mechanism of action and or indication. So called comparator modelling based on public domain data (individual and study-arm level) can help to create robust models for extrapolation.</p> <p>Comment:</p>	Partly accepted. The concept paper will not be amended. The principles will be taken forward in the reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		For the similarity, we would suggest to include 'how to utilize the similarity degree between source and target populations in determining the feasibility (or to what extent) of extrapolation' in the plan.	

4. RECOMMENDATIONS

Page 6/7 (Lines 177-188)	1	<p>Comment:</p> <p>It would be useful to expand Section 4 in the reflection paper and provide more details on the envisioned form of the database of examples and inventory of rules.</p> <p>Comment:</p> <p>The concept paper indicates discussion and harmonization with FDA. Going forward, if this approach is adopted in the EU, it will be important to harmonise across other agencies too, e.g. via ICH in order not to lose the advantage that extrapolation would bring to efficient global medicines development.</p>	<p>Accepted.</p> <p>Partly accepted. The FDA has worked on extrapolation of efficacy to the paediatric population. The scope of the reflection paper is wider.</p>
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5. TIMETABLE and 6. RESOURCE REQUIREMENTS

Page 6-7/7 (Lines 189-196)	1	<p>Comment:</p> <p>The timetable and resource requirements are given for the reflection paper but not for the other items (database of examples, inventory of rules, etc.). It would be interesting to have the Agency thoughts and plans on how these would be implemented and when they would come together.</p>	<p>Partly accepted. All relevant EMA committees and working parties will be consulted during the development of the reflection paper.</p>
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5. TIMETABLE and 6. RESOURCE REQUIREMENTS

		Comment: The concept paper has not been agreed/adopted by the PRAC (presumably since it pre-dates its formation). We assume that there are plans for including their input.	
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9: REFERENCES

Page 7/7 (Lines 204-218)	1	Comment: Please consider adding an explicit reference to the ICH E5 Guideline in the reflection paper, since it provides important guidance for and contains general principles of extrapolation.	Accepted.
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