EMA/478467/2016

Public workshop on extrapolation of efficacy and safety in medicine development across age groups

Outcome of a multi-stakeholder meeting with experts and regulators held at EMA on Tuesday 17 May and Wednesday 18 May 2016

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1. Introduction

The Paediatric Regulation (EC) 1901/2006 came into force in the European Union (EU) on 26 January 2007. The Regulation aims to ensure that medicines for use in children are of high quality, are ethically researched and are authorised appropriately.

Extrapolation of data aims to optimise the involvement of children in clinical studies, one of the objectives of the European Union Paediatric Regulation, by predicting how a medicine may work in children and adolescents on the basis of studies conducted in adults or other paediatric populations with the specific investigational product and/or with medicines with similar mechanism of action.

Following the Regulators Experts meeting on Extrapolation held on 30 September 2015, the EMA published a draft reflection paper on extrapolation of efficacy and safety in paediatric medicine development. The draft reflection paper outlines a systematic approach to extrapolation of data from adults or other paediatric populations to children that is considered scientifically sound and reliable to support the authorisation of a medicine. The framework sets out when, to what extent, and how extrapolation can be applied and validated.

However, accepting and implementing extrapolation for medicine development is challenging for many reasons. Hence, to explore ways of developing further the framework and appropriate methodological tools, EMA convened a multi-stakeholder meeting on 17 May and 18 May 2016, attended by experts including clinicians, pharmacologists, pharmacometricians and statisticians from leading academics and researchers, representatives from patients and healthcare professionals organisations, small and large pharmaceutical companies, national competent authorities (NCAs) and non-EU competent Authorities.

Additionally, the revision of the ICH E11 (Clinical Investigation of Medicinal Products in the Paediatric Population) is ongoing with a focus on extrapolation. Thus, it is important to provide drug developers with clear and compatible guidance specific to global product development and licensing of paediatric medicines.

This report summarises the main ideas and solutions proposed during the meeting, the outcome will contribute to the further development of the draft refection paper which is expected to be released for public consultation by the end of October 2016 and to the implementation of the Extrapolation Framework in relevant procedures.

Main topics discussed

- Methodological tools potentially applicable to the EMA extrapolation framework
- Challenges and opportunities from the different stakeholders' for the clinical, statistical and pharmacometrics disciplines
- Main proposals for regulatory tools and impact on research and development for developing and implementing the extrapolation framework

2. Use of the extrapolation framework and its tools

Stakeholders welcomed and supported the EMA extrapolation framework which proposes an explicit and systematic approach to extrapolation that sets out i) when, ii) to what extent, and iii) how extrapolation can be applied and validated.

It is noted that the pharmaceutical industry would also welcome specific guidance on how to use the available methodological tools and regulatory pathways for decision-making; however regulators

clarified that to have more specific guidance on how to use the tools might restrict innovative developments to overcome the challenges faced in paediatric drug development. Instead of a one size fits all approach, drug developers are invited to discuss the clinical particularities and evaluate if needed several scenario proposals for paediatric developments

It was agreed that Developers are encouraged to approach the EMA at the early stage of the development to discuss different pathways for the paediatric development (including adults where appropriate) and balance them against their respective risks and potential gains in efficiency. Dialogue should take place, for example, through safe harbours such as the scientific advice working party.

At the meeting, stakeholders identified the need for further clarifications in the Reflection Paper on the use of the tools in the context of extrapolation and in the context of borrowing evidence. Some examples and more specific references to the tools available and their use to support extrapolation will be provided in the final paper.

It was also generally agreed that regardless of the context of extrapolation as a starting point knowledge needs to be systematically quantified, synthesised and presented. A careful consideration for the right questions to be answered by the studies to be designed should be part of the early development strategy. It was reinforced that the adults' studies should be designed with children and knowledge gaps to be addressed in mind.

Another major topic discussed was related to the planning and validation of the assumptions.

Solutions such as a classification system for the assumptions to be made were proposed by the EFPIA MID3 Workgroup. The proposal was welcomed by the audience but regulators made a call for having not only assumptions but also the uncertainties explicitly stated at an early stage of the development. Most importantly, this exercise should complement a systematic analysis and identification of the areas that are important for decision-making where knowledge is currently lacking, so that studies can be targeted to answer the key scientific areas of interest.

Specific points considered central to the discussion related to uncertainties and the decision-making, particularly how to link the extrapolation plan and the extrapolation concept in order to confirm the assumptions and address uncertainties. While it is acknowledged that some 'residual' uncertainty always remain at the time of licensing, the EMA highlighted it considers that it is to the utmost importance to summarise all the uncertainties and identify which ones are critical and need to be addressed to support an authorization in the paediatric population. The concept of learning and confirming is central in paediatric development, thus the confirmation / validation requirements may change accordingly to what is known over time in the source population regarding PK-PD-Efficacy.

In view to facilitate the decision- making processes, the concept of regulatory impact proposed in the framework for Modelling and Simulation in Regulatory Review According to the impact on regulatory decision during the EMA EFPIA-EMA Modelling and Simulation Workshop in 2011 (Role of Modelling and Simulation in Regulatory Decision Making in Europe T. Shepard) was identified as to be extended beyond modelling and simulation to extrapolation. The definitions of low, medium and high impacts should however be harmonised across stakeholders.

Another topic touched upon was the need for models to clarify the prior for an informed decision such as how to translate uncertainties into the strength of the prior. Different tools available to facilitate the extrapolation of efficacy are MID3, innovative statistical methods and innovative trial designs (e.g. adaptive). In situation where pharmacometrics may have high risks and uncertainties it should be mitigated with statistical methods while planning and designing the studies.

In addition it was agreed that each tool should be adapted according to the purpose of their use; meaning that they might have a different impact in terms of risk and uncertainties if used at planning

or validation stage, hence these aspects should be clarified in the Reflection paper. Pharmaceutical industry would also welcome specific guidance on the choice of tools to be used for extrapolation and definition of success criteria.

With regards to designing studies, regulators reiterated that different clinical trial design and success criteria can be acceptable but sound statistical principles behind the selected strategy will remain important, for example pre-specification of design and analysis or quantification of the risk of false positive/false negative decisions. However it is also recognized that scientifically justified pharmacological principles may not require independent verification in prospective studies and may mitigate the statistical requirements at planning and analysis phase. Collaboration between statisticians, pharmacometricians and clinicians should be facilitated to develop and improve methods to structure the prior knowledge and source data in view to make informed decisions.

The topic of statistical methods in the design of PK/PD studies was addressed. PK/PD studies may have different objectives, for example they can be designed for the purpose of investigating safety and dose finding for subsequent efficacy studies in the target population or they can aim at validating extrapolation of PK and PD assumptions. Thus according to the aim of the studies, stakeholders agreed that there is the need to optimize the design of PK/PD studies and it was also agreed that this is an area that would benefit from further research and extended use in practice when extrapolation of efficacy is acceptable.

One of the concerns from the developers is related to the possibility to have a failed extrapolation approach and the need to update the extrapolation concept and revised the extrapolation plan accordingly. There seems to be the need to clarify the concept of learning and confirm exercise within the context of modelling and simulation and the concept of iterative loops for the purpose of extrapolation.

Methodological tools – main stakeholder agreement and proposals

- The EMA extrapolation framework which aims at proposing an explicit and systematic approach to extrapolation is welcome and supported;
- It is recommended to have early dialogue with health authorities and propose risk based scenario approaches for paediatric developments;
- Different clinical trial design and success criteria can be considered but statistical and pharmacological principles will remain important in the regulatory decision making;
- There is the need to align regulators, pharmaceutical industry and academia on the required tools for the purpose of extrapolation and in the context of borrowing information. Scientific Advice, early paediatric interactions, qualification of novel methodologies are proposed as communication platforms.
- Approaches to quantification would benefit from further research, refinement and experience:
  - How to summarise, use and communicate information generated to date at submission;
  - To develop models to clarify the prior for an informed decision such as how to translate uncertainties into the strength of the prior;
  - How to specify and justify success criteria, in particular if working outside the traditional frequentist RCT space where a p-value of less than 0.05 is the expected hurdle;
  - Identification of the required evidence to validate assumptions made.
- Stakeholders agreed that there would be some benefit in optimizing the design of PK/PD studies in particular when extrapolation of efficacy is acceptable.

3. Regulatory processes

The main objective of the Paediatric Regulation (EC) No 1901/2006 aims to ensure that medicines for use in children are of high quality, are ethically researched and are authorised appropriately.

The Annex on key elements from the EC Guideline on the format and content of applications clearly lists all the elements to be included in the Paediatric Investigation Plan. It was emphasised by regulators that extrapolation concepts requires an iterative approach that needs to be reflected in the PIP life-cycle. Careful considerations of the reflection and planning for the iterative loops should be part of the early development strategy and discussed with regulators early in the process to allow requirements to be adapted accordingly. Dialogue, for example, through safe harbours such as the paediatric early interactions and more appropriate use of the scientific advice procedure is needed particularly when adults and children need to be discussed together. Developers highlighted that they would welcome a joint PIP – Scientific Advice procedure and more specific guidance through what regulatory procedure sponsors would need to seek agreements. A joint global regulatory procedure could be envisaged by regulators.

It was agreed that better planning for the use of extrapolation approaches and greater collaboration with regulators ahead of the initiation of the pediatric clinical studies should results in optimizing and streamlining the life-cycle of the PIP.

It was also noted that developers expressed the concern around introduction of uncertainties in relation to securing compliance check and opportunity for reward when extrapolation approaches are being used, particularly in the context of failed studies.

With regards to the implementation some practical challenges remain to be discussed, such as need for novel reporting structures as part of an Extrapolation Study Report.

Another point touched upon was whether the possibility to agree PIPs with learning objectives on the systems knowledge could be considered in view to encourage a structured data collection and information sharing.

It was highlighted that all the proposals above should be feasible within the legislative framework in the EU on paediatrics laid down in Regulation (EC) No 1901/2006.

Regulatory process – main stakeholder proposals

- The iterative aspect of extrapolation reflects a regulatory need to be adequately reflected in the paediatric investigation plan. To allow requirements to be adapted according to the planned iterative loops, early development strategies should be discussed with regulators through the existing pathways such as PDCO early interactions and/or scientific advice.
- Stronger collaboration between SAWP and PDCO should be considered, particularly for the cases where adults and children will be planned together.

4. Research and development

There was a consensus from the workshop that extrapolation in the paediatric population is still at learning stage.

Similarly, while it was considered that extrapolation might permit to reduce the number of paediatric trial participants, it was acknowledged that the need for context data will increase specifically related

to developmental growth and maturation, pathophysiology (from modelling, surrogacy, adults, historical cohorts, registries, epidemiology, real world evidence data, genomic variability sources etc.).

Consequently it was agreed that the identification of the evidence necessary to inform the paediatric drug development program will require considerations for additional systematic collection of data in adults and children during these learning stage; not necessarily only within a same development but across developments (e.g.: precompetitive collaborative initiatives across companies or data sharing).

Stakeholders highlighted that they would welcome initiatives to address some of the challenges related to the investigation of medicinal products in the paediatric population funded under public/private partnership that could allow research at the disease level for instance. Particularly when it comes to the younger paediatric age groups due to the maturational changes anticipated.

Another area that could benefit from further research and harmonisation would be the application of the extrapolation framework at the therapeutic area level where there is the need to develop age appropriate tools, development of surrogate endpoints (such as for younger patients or other subpopulations) while ensuring global compatibility.

To foster the development of appropriate methodological tools, under the FP7 Call – Health projects the EU has funded three international multidisciplinary research consortia aiming at the efficient assessment of the safety and/or efficacy of a treatment for small population groups including drug development for children. Representatives from the 3 projects are involved in the extrapolation activities at EMA and were invited to present the projects and out their output are fitting with the regulatory needs. The projects ASTERIX (Advances in small trials design for regulatory innovation and excellence), IDEAL (Integrated design and analysis of small population group trials), InSPiRe (Innovative methodology for small population research) were initiated in 2014. All three projects have created networks of clinical trial experts involving all relevant stakeholders such as academia, industry, regulators and patient advocacy groups. The aim of these projects is to identify the difficulties in clinical research in small populations and identify promising approaches to efficiently overcome them.

It was agreed that the extrapolation framework with its approaches and tools will create the need to develop new models for innovative development. One of the tools to be considered is the model of Real World Data that can help to overcome some of the challenges faced by paediatric development, for instance in supporting the validation of assumptions related to residual uncertainties at the time of paediatric licensing. Henceforth the planning for collection of structured data is particularly important to be set up *a priori* in view to successfully implement the concept of an iterative loop across developments.

While the pharmaceutical industry and other stakeholders acknowledged the need for high standards in innovative approaches for paediatric development, Patients' groups have not yet developed a unique position with regards to extrapolation. The main points of tensions are to find the adequate balance between early access, sufficient exposure for the safety, and ethical aspects. Hence the involvement and participation of patients, parents and their organizations as well as of paediatric research networks in the conception, design and conduct of research is strongly recommended since it is recognized to improve the ethical quality of paediatric studies.

As with regards to Healthcare professionals' representatives, their main request is to improve problems related to the use of off-label drugs in the paediatric population. There is sufficient evidence that harm actually does occur and is under- reported with the off-label use in the paediatric population. This supports measures to improve information on medicines used in children (October 2004, EMEA/126327/2004 Evidence of harm from off-label or unlicensed medicines in children). The gaps could be filled by either collecting PK and PD data for the off-label drugs and selected outcome measures on efficacy and safety when needed or to generate the necessary information for paediatric

labelling by the use of innovative approaches when possible (use of existing evidence optimised by modelling and simulation).

Research and Development – main stakeholders agreement and proposals

- To achieve the aims of the use of extrapolation approaches in the paediatric population there is the need to foster the development of methodological tools. The use of public/private partnerships should be considered, particularly for developing ways for systematic data collection in view to increase the knowledge in the paediatric population related to maturational changes, development of age appropriate tools and surrogate endpoints.
- To improve the knowledge and the planning for data collection in paediatric registry data or real word evidence the structure of the data collection should be considered *a priori*.
- Extrapolation is at learning stage and there are many initiatives on going within academia, pharmaceutical industries and regulatory authorities. There is the need to ensure alignment on the requirements and standards of the methodological tools to be used and synergies of the ongoing projects developing new tools, methods or endpoints. To develop an extrapolation community across disciplines and stakeholders would facilitate communication and a more efficient way to progress research and development.

5. Conclusions

For ethical and feasibility reasons there was agreement that there is a need to be innovative in the area of paediatric development. Paediatric medicines development is a driver for Model Informed Drug Development Decision (MID3) to aid better plans and decision, and is helping to move science forward in learning and better understanding how to use and develop in silico trial methods.

This summary covers the main proposals related to the methodological tools, regulatory processes and research and development from stakeholders for developing and implementing the extrapolation framework of efficacy and safety in medicine development across age groups.

Recurring themes touched upon at the meeting include the need for early interaction and more specific guidance from regulators, greater harmonisation between stakeholders in various aspects within research and development areas, as well as development, acceptability and validation of new methodological tools.

There is a general agreement that quantitative challenges will be best addressed by a collaborative effort of Pharmacometrics, Statistics, and Clinical disciplines and need to be implemented by all disciplines across stakeholders.

Regulators welcome the contribution from stakeholders that will help on developing the use of extrapolation for generating data in the paediatric population and is looking forward to further and closer collaborations with the stakeholders.

This contribution, as well as subsequent proposals will be reflected in the version of the draft Reflection paper to be released for public consultation in the last quarter of 2016.

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European Medicines Agency Secretariat:

- Cécile Ollivier – Paediatric Office (ICH E11 working group)
- Efthymios Manolis – Scientific Advice Office
- Andrew Thomson – Biostatistics and Methodology Support Office
- Kevin Blake – Clinical Pharmacology and non-clinical Support Office
- Richard Vesely – Head of Rheumatology, Respiratory, Gastroenterology and Immunology Office

Committee and Working Parties / National Competent Authorities:

- Tomas Salmonson, Committee for Medicinal Products for Human Use (CHMP Chair)
- Rob Hemmings, Scientific Advice Working Party (SAWP Chair)
- Dirk Mentzer, Paediatric Committee (PDCO Chair) - ICH E11 working group
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- John Watson (Zogenix) EUCOPE
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