Concept paper on extrapolation of efficacy and safety in medicine development
Draft

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1. Introduction

Extrapolation may be generally defined as: 'Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.

The primary rationale for extrapolation is to avoid unnecessary studies in the target population for ethical reasons, for efficiency, and to allocate resources to areas where studies are the most needed. Alternatively, in situations where the feasibility of studies is restricted, extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources.

Extrapolation from adults to children is a typical example but extrapolation may be applied in many other areas: e.g. i) between population subsets, based on age (down and up age subsets), growth, maturation, sex, pregnancy, co-morbidities, impaired organ function, ethnic intrinsic and extrinsic factors; ii) between disease subtypes or stages, different diseases, symptoms; iii) between medicines, within and between classes; iv) from animal studies to humans; v) from healthy volunteers to patients.

The concept paper is intended to discuss the need and possibility to develop a framework for extrapolation approaches that are considered scientifically valid and reliable to support medicine authorisation. The framework shall set out a structured approach to be followed for each extrapolation exercise to improve interactions with stakeholders and to standardise the decision making across EMA committees. Since the application of extrapolation varies by population, therapeutic area, and medicinal product, an inventory of approaches and case examples shall be collected.

2. Problem statement

Extrapolation of efficacy and safety is used implicitly in many regulatory decisions, for example when extending conclusions from trial populations to the general population, different population subsets or between indications. The objective of this concept paper is to develop a framework for an explicit and systematic approach which sets out i) when, ii) to what extent, and iii) how extrapolation can be applied. The framework may include the following elements:

- Development of an extrapolation concept: this would build on a systematic synthesis of available data (in vitro, preclinical, clinical), and 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 and target populations.

- Extrapolation plan, proposing a reduced set of supportive studies in the target population in accordance with the extrapolation concept.

- 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); or, if the concept cannot be validated, update of the extrapolation concept and plan.

- Extrapolation: interpretation of the limited data in the target population in the context of information extrapolated from the source population(s).

There are several gaps in knowledge and issues that need to be resolved to develop a framework for extrapolation, including:

- to define the impact of extrapolation in drug development and regulatory review;

- to consider the clinical context: how to account for feasibility and ethical restrictions for studies in specific populations;

- how defining and quantifying similarity of disease (progression), of PK/PD, of clinical response to treatment and safety aspects;

- how deciding on the quality and quantity of existing data and types of study designs to support the extrapolation concept;

- how weighing the strength of prior information;

- how integrating expert judgement in the extrapolation concept;

- how quantifying the uncertainty of extrapolation assumptions;

- how validating assumptions in the extrapolation concept;

- how dealing with uncertainty and risk;

- how analysing and reporting post-authorisation data to support extrapolation.

3. Discussion (of the problem statement)

The FDA published an algorithm which provides an assumptions-based framework for the extrapolation of efficacy from adults to the paediatric population (FDA 1994): Based on US law, the *Paediatric study decision tree* allows extrapolation if there is sufficient similarity of both i) disease progression and ii) response to intervention between source and target population. If the exposure-response relationship of the medicinal product is assumed to be similar, only PK studies for dose determination and safety studies are required. If the exposure-response relationship is unclear, additional PK/PD studies are required. If no similarity can be assumed with reasonable certainty, a full study programme in the target population with PK and/or PK/PD studies, and efficacy and safety studies is required. Safety studies are considered always necessary as safety profiles may differ from those in adults.

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)'.

The EMA Extrapolation Working Group sees the need to go beyond these documents and to discuss the possibility to develop an expanded and refined algorithm for extrapolation in all areas of medicine development. The following framework is proposed:

A. Clinical context

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). These situations are frequently intertwined but should be considered separately for a structured and transparent approach. This discussion is seen as a relevant background to a discussion on the scientific validity of the extrapolation concept that is explored below.

B. Development of an extrapolation concept

- Biological and pharmacological rationale

Using a checklist, the following items should be assessed in source and target populations:

- Similarity of disease (subtypes based on aetiology, pathophysiology, clinical manifestation, progression (indicators)).

- Similarity of medicine disposition & effect (mode of action, PK, PD).

- Similarity and applicability of clinical efficacy and safety endpoints.

Data sources to be reviewed: in vitro, preclinical, epidemiological studies, diagnostic studies, clinical trials and observational studies with standard therapy, the innovative medicine, or similar medicines.

- Quantitative evidence

- Disease progression: Disease models could be used to characterise differences in disease progression between groups.

- 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.

- Clinical response: quantitative synthesis or modelling of all existing data (in-vitro, preclinical and clinical) to predict the degree of similarity in clinical response (efficacy, some safety aspects) between source and target population.

- Extrapolation concept:

Explicit hypothesis on the expected difference 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 concept will require expert interpretation and judgement to weigh the existing evidence and fill in knowledge gaps.

The rationale should be given for the selection of an extrapolation strategy among the following general categories:

- No extrapolation: full development programme in the target population.

- Partial extrapolation: reduced study programme in target population depending on magnitude of expected differences and certainty of assumptions.

- Full extrapolation: some supportive data to validate the extrapolation concept.

C. Extrapolation plan

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. In general, the data generated in the target population should validate the extrapolation concept and complement those that may be extrapolated from the source population. Studies should focus on those complementary areas, e.g. age subsets, where the largest differences to the source population are expected.

Two principal scenarios may be considered:

- Bridging using solely PK or PK/PD in the target population to extrapolate efficacy. This approach would be based on the concept that matching drug exposure or exposure response to the source population will be associated with similar efficacy in the target population.

- 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 following are examples of approaches to extrapolation that have been used in Paediatric Investigation Plans:

- PK/PD studies only.

- Dose-ranging or dose-titration studies.

- Non-controlled 'descriptive' efficacy and/or safety study.

- Controlled study but arbitrary sample size.

- Larger significance level, lower coverage probability of confidence intervals.

- Acceptance of surrogate endpoints for the primary analysis.

- Interpolation (bridging), e.g. between age subgroups.

- Modelling prior information from existing data sets (Bayesian models, meta-analytic predictive).

D. Validation

The emerging data in the target population shall be used to validate the extrapolation concept (model check):

- To confirm the PK and PD model assumptions and predictions.

- To validate the modelling approach used for extrapolation.

- To confirm the predicted degree of similarity (or understanding) in disease progression or clinical response (efficacy, safety).

If the data do not confirm the extrapolation concept, the concept needs to be **updated** by the emerging data regarding the true extent of similarity and, hence, ability to extrapolate. Consequently, the need to generate more data in the target population should be assessed and the **extrapolation plan adjusted**. This may be an iterative process using adaptive designs, particularly when moving into successive population subsets, e.g. down age subsets.

E. Extrapolation:

Based on the extrapolation concept, the data generated in the target population will not be self-standing to support conclusions on dosing, efficacy and safety of the medicines. Hence, the data need to be interpreted in the context of information extrapolated from the source population(s).

F. Dealing with uncertainty and risk:

The more (assumed) similarities there are between source and target population, the more limited will be the data set generated in the target population and conclusions will rely on information extrapolated from the source population(s). At the same time, there will be fewer data available to validate the extrapolation concept with a potential to increase the risk of a false conclusion regarding the efficacy and safety of the medicinal product in the target population if the underlying basis for the extrapolation is incorrect. To consolidate the reliability of conclusions based on extrapolation, collateral measures and criteria could be implemented such as:

- Biological plausibility supported by in vitro, preclinical or clinical data.

- Iterative loops of model building and data generation.

- Concordant responses on different endpoints.

- Prospectively planned meta-analysis including future trials.

- Joint analysis of overall development program with covariate analysis, e.g. age.

- Confirmation by (cumulative) post-authorisation data.

- Validation of extrapolation approaches over several developments in related conditions, or related medicines.

- Others.

With increasing experience with extrapolation approaches over several development programmes in specific therapeutic areas or medicines, the requirements for individual developments may change.

4. Recommendation

The EMA Extrapolation Working Group, including in particular representatives from PDCO, CHMP, SAWP, COMP and methodologists recommends drafting a reflection paper on extrapolation of efficacy and safety in medicine development.

A database of case examples from various therapeutic areas shall be generated. Eventually, an algorithm for extrapolation (or set of approaches) and inventory of methodological rules should be developed.

A checklist to be part of both application documents and evaluation documents at PDCO and SAWP shall be developed. Consultation of and contribution from stakeholders (e.g. pharmacologists, methodologists, industry, academia) and discussion and harmonisation with FDA shall also be implemented.

The final goal is to develop guidance on extrapolation for medicines development.

5. Proposed timetable

The proposed timeframe is to develop a reflection paper within 12 months of publication of the Concept Paper.

6. Resource requirements for preparation

Preparation for the reflection paper will be done by virtual meeting. It is anticipated that one face to face meeting will be required. The preparation will involve all relevant Committees and Working Parties (Biostatistics, Scientific Advice...). The document is predicted to be discussed on two of their respective meetings.

7. Impact assessment (anticipated)

It is anticipated that this document will lead to an improved standard of assessment and decisions on extrapolation at EMA. Its aim eventually to result in better utilisation of patient involvement in clinical research, and in guidance for stakeholders.

8. Interested parties

EMA Committees and Working Parties, pharmaceutical companies, academia, patients and international regulatory partners.

9. References to literature, guidelines, etc.

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