Paediatric Investigation Plans
and the EMA Extrapolation framework

GRIP Workshop, Glasgow, June 2013

Christoph Male
Medical University of Vienna, Austria
Austrian Delegate in the Paediatric Committee (PDCO)

Disclaimer: The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.
Synopsis

• Paediatric Investigation Plan
• Extrapolation definition and rationale
• EMA extrapolation framework
• Discussion
**EU Paediatric Regulation**
(EC No 1901 & 1902/2006)

- **Requirement:** Paediatric Investigation Plan (PIP) for all new drugs & new indications of authorized drug or deferral or waiver

- **Reward:** patent extension

- **Paediatric Committee (PDCO) at EMA**

- **Collateral measures**
  e.g. Grants for paediatric studies into off-patent drugs
EU Paediatric Regulation

Objectives:

- high quality, ethical research into medicines for children
- increase availability of authorised medicines for children
- improved information on medicines
- without subjecting children to unnecessary studies
Paediatric Investigation Plan (PIP)

Details of all measures of pharmaceutical and clinical development to support the authorisation of a drug for children

- Formulation
- Toxicology, PK, PD, carcino, genotox juvenile animals
- Safety - Proof of concept
- Dose-Finding - PK
- Efficacy
- Safety issues
PIP procedure

- PIP proposed by company
- At the end of phase I of adult development
- Modified and agreed/declined by PDCO
- Decisions are published
- Modifications possible
- Legally binding for company and authorities
Key considerations for PIPs

- Paediatric indication(s)
- Paediatric age groups
- Timing of paediatric studies in relation to adult development
- How much extrapolation is possible?
  - from adults to children
  - from other sources
  - between paediatric age groups

PIP
waiver
deferral

• Supporting data
• Types of studies
• Other measures
EMA extrapolation working group

• Cross-committee working group (PDCO, CHMP, COMP, SAWP, Biostatistics WP)

• Objective: to develop framework for an explicit and systematic approach to extrapolation, setting out i) when, ii) to what extent, iii) how to apply extrapolation

• Need to go beyond existing guidelines for expanded and refined algorithm(s)

• 'Extrapolation concept paper' published
22 June 2012
EMA/129698/2012
Human Medicines Development and Evaluation

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

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreed by Scientific Advice Working Party</td>
<td>25 April 2012</td>
</tr>
<tr>
<td>Agreed by Biostatistic Working Party</td>
<td>15 May 2012</td>
</tr>
<tr>
<td>Agreed by PK Working Party</td>
<td>30 May 2012</td>
</tr>
<tr>
<td>Agreed by COMP</td>
<td>10 May 2012</td>
</tr>
<tr>
<td>Adoption by PDCO</td>
<td>16 May 2012</td>
</tr>
<tr>
<td>Adoption by CHMP</td>
<td>24 May 2012</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>29 June 2012</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>30 September 2012</td>
</tr>
</tbody>
</table>
Extrapolation definition

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 minimizing the need to generate additional information (types of studies, number of patients required) to reach conclusions for the target population.
Areas of extrapolation

- Population subsets
  - Age (down / up age subsets)
  - Growth, maturation
  - Sex; pregnancy
  - Comorbidities
  - Ethnicity

- Disease subtypes / stages; different diseases

- Drugs (within / between classes)

- Species (preclinical toxicity and pharmacology)
Rationale

1. Avoid ‘unnecessary‘ studies
   - Ethics
   - Efficiency
   - Ressource allocation – focus on areas where studies are most needed

2. Feasibility restrictions
   - Apply extrapolation principles for rational interpretation of limited evidence in the context of data available from other sources
Extrapolation framework
Stepwise approach

Basic consideration:
- similarity of disease / progression
- similarity of response to treatment

1. Extrapolation concept
   a. Biological/pharmacological rationale
   b. Quantitative evidence, model building
   c. Hypothesis

2. Extrapolation plan
   - Reduction of data requirements

3. Validation

Adapting  Learning
Extrapolation concept

A. Biological/ pharmacological rationale

• Similarity of disease
  - Aetiology, pathophysiology
  - Clinical manifestation
  - Course, progression (indicators)

• Similarity of drug disposition & effect
  - mode of action
  - PK
  - PD

• Similarity and applicability of clinical endpoints
  • Efficacy
  • Some safety aspects
Extrapolation concept
Emphasis on quantifying the system for decision making

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, body size, maturation, age and other important covariates (such as age, renal and hepatic function)

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

Pharmacokinetics
- Physiologically-based PK modeling
  - Systemic exposure
  - Biophase distribution

Pharmacodynamics
- Mechanism-based PD modeling
  - Receptor theory
  - Dynamical Systems analysis

Disease
- Mechanism-based disease modeling
  - Disease system analysis

Clinical outcome
- “Intrinsic” and “Operational” Efficacy/Safety

Extrapolation concept

C. Hypothesis / model

- Explicit (quantitative) statement on the expected differences in response to the drug between target and source population

- Assumptions and uncertainties to be specified
Can you find the difference?
## Extrapolation plan

<table>
<thead>
<tr>
<th>Differences between populations</th>
<th>Uncertainty of hypothesis</th>
<th>Extrapolation</th>
<th>Study programme (target population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>high</td>
<td>NO</td>
<td>➢ full development programme</td>
</tr>
<tr>
<td>Moderate</td>
<td>some</td>
<td>PARTIAL</td>
<td>➢ reduced study programme dependent on magnitude of expected differences and/or degree of uncertainty</td>
</tr>
<tr>
<td>Small</td>
<td>low</td>
<td>FULL</td>
<td>➢ some supportive data for validation</td>
</tr>
</tbody>
</table>
Extrapolation plan

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 expected degree of similarity

- Should validate the extrapolation concept
- Complement the information extrapolated from source population(s)
- Focus on complementary areas where largest differences expected
Inventory of extrapolation approaches used in PIPs

- PK/PD studies only (including M & S)
- Dose-ranging or dose-titration studies
- Non-controlled ‘descriptive’ efficacy / safety study
- Controlled study but ‘arbitrary‘ sample size
- Larger significance level, lower %age confidence intervals
- Studies powered on surrogate endpoint
- Intrapolation (bridging)
- Modelling prior information from existing data sets (Bayesian, meta-analytic predictive)
- etc
Validation

Use emerging data to validate

• PK and PD model assumptions
• Modelling approaches used for extrapolation
• Predicted degree of similarity in disease progression and response to treatment

➢ Revisit assumptions and refine EP concept and plan
➢ Iterative process using adaptive designs, particularly when moving into successive population subsets (age)
Mitigating uncertainty and risk

The more extrapolation → the fewer data for validation

⇒ risk of false conclusions

➢ Collateral criteria and measures:
  • Biological plausibility (in-vitro, preclinical and clinical data)
  • Iterative loops of model building and data generation
  • Concordant responses on different endpoints
  • Prospectively planned meta-analysis including future trials
  • Confirmation by post-authorisation data
  • Validation of extrapolation approaches over several developments in related conditions, or related medicines
  • etc.
Challenges

How to quantify similarity?
Many challenges to be resolved …

- Dealing with feasibility and ethical restrictions
- Quantifying similarity of disease (progression), of PK/PD, of clinical response to treatment and safety aspects
- Judging quality and quantity of existing data and types of study designs to support the extrapolation concept
- Integrating expert judgement in the extrapolation concept
- Quantifying the uncertainty of extrapolation assumptions
- Validating assumptions in the extrapolation concept
- Analysing post-authorisation data to support extrapolation
Why extrapolation is so controversial?

Understanding the biological systems is difficult

- Pathophysiology
- Physiology
- Pharmacology
- Toxicology

New Tools are needed

- Analytical Assays
- In vitro models
- Animal models
- Biomarkers
- Endpoints
- Data analysis tools
Why extrapolation is so controversial?

Regulatory Challenges:

Manage **uncertainty and risk** (increased vs 2 randomised control trials which is the current gold standard)

**Clinical context** (ethical issues, medical need, availability of other treatment, feasibility of studies)

**Lack of standardisation** of methods (experimental design, data analysis tools, surrogate markers) and decision criteria for extrapolation

**Quality of data**

**Regulatory Precedent**
Modeling and Simulation: Role in Drug Development Program/Regulatory Decision Making

Level 1. Used to summarise data (SPC, PIL), optimal program, study design

Level 2. Used for optimal program, study design with restriction of population, intrinsic, extrinsic factors, etc.

Level 3. Used to replace clinical trials.

Framework from Rob Hemmings, Statistics Unit Manager, MHRA
Presented at EMA-EFPIA M&S workshop
Modelling and Simulation in PIPs

Based on the published research:
M&S abundant in PIP submissions, proposed for dose finding, study optimisation and analysis, not as a tool to navigate in the decision tree.

Role of modeling and simulation in pediatric investigation plans.
Manolis E, Osman TE, Herold R, Koenig F, Tomasi P, Vamvakas S, Saint Raymond A.
Regulatory Follow-Up on Extrapolation

EFPIA EMEA Workshop on Modelling and Simulation
30/11-1/12 2011 EMEA, London, UK

EMA Extrapolation Group

EMA Modelling and Simulation Working Group
Conclusions

• Extrapolation is welcomed as a means to save patients and resources (i.e. target research where mostly needed), of special importance in PIPs

• Currently case-by-case approach but EMA is working on a more standardised framework

• Easier if the biological system is well characterised and qualified biomarkers exist

• New and standardised tools are needed to advance science and regulatory assessment of extrapolation

• Vision: use of M&S as platform to facilitate extrapolation

• Ultimately extrapolation is a clinical decision

• Early and close interaction with regulators
Extrapolation Framework

1. Clinical Context
   - Rationale why extrapolation is considered rather than a complete set of prospective studies (e.g. feasibility, ethical issues, clinical practice, strong scientific rationale)

2. Extrapolation Concept
   - Develop quantitative assumptions on the similarity of the disease, PK/PD and response

3. Extrapolation Plan
   - Define studies and tools (e.g. M&S) needed to complete the knowledge gap and to validate the assumptions

4. Validation
   - In light of emerging data test previous assumptions and if needed modify assumptions

5. Extrapolation
   - Interpretation of the limited data in the target population in the context of information extrapolated from the source population

6. Dealing with uncertainty and risk
   - Evaluate impact of violation of the assumptions. Define strategies to mitigate risks and further evaluate assumptions
Next steps

- EP concept paper – input from external consultation
  - Reflection paper
- Checklist for submission documents
- EP working group to review individual submissions
  - Database of case examples for various therapeutic areas
  - Algorithm (or set of approaches) for extrapolation
  - Harmonisation with FDA
  - Guidance document
Many thanks to colleagues

Eftymios Manolis

EMA Extrapolation Working Group

EMA Modelling and Simulation Working Group
There are two types of people in this world:

Those who can extrapolate from incomplete data
Back-up
FDA decision tree for extrapolating efficacy to the paediatric population

Is it reasonable to assume that children, when compared to adults, have a similar (a) disease progression and (b) response to intervention?

- Yes to Both
  - Is it reasonable to assume a similar exposure-response (ER) in children, when compared to adults?
    - Yes
      - Conduct PK studies in children which are designed to achieve drug levels similar to adults and then conduct safety trials at the proper dose.
    - No
      - Is there a pharmacodynamic (PD) measurement that can be used to predict efficacy in children?
        - Yes
          - Conduct PK/PD studies to establish an ER in children for the PD measurement, conduct PK studies to achieve target concentrations based on ER, and then conduct safety trials at the proper dose.
        - No
          - Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.

- No to Either
Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs

WHAT'S KNOWN ON THIS SUBJECT: Extrapolation of efficacy, an approach first proposed in 1994, can increase the efficiency of pediatric drug development. Little has been published on its practical application and whether it can achieve the objectives of increased efficiency and increased pediatric drug labeling.

WHAT THIS STUDY ADDS: Extrapolation can be used successfully to decrease the number of pediatric patients and studies required for pediatric drug development. Approaches have changed over time with growing knowledge and experience regarding the assumptions underlying extrapolation for particular therapeutic classes and indications.

AUTHORS: Julia Dunne, MD, FRCP, a William J. Rodriguez, MD, PhD, a M. Dianne Murphy, MD, a B. Nhi Beasley, PharmD, b Gilbert J. Burckart, PharmD, b Jane D. Fille, MD, a Linda L. Lewis, MD, a Hari C. Sachs, MD, f Philip H. Sheridan, MD, g Peter Stork, MD, h and Lynn P. Yao, MD a

Office of Pediatric Therapeutics, Office of the Commissioner, Divisions of aCardiorenal Products, dAnesthesia, Analgesia, and Rheumatology Products, eAntiviral Products, fPediatric and Maternal Health Staff, gNeurology Products, hPulmonary and Allergy Products, and eOffice of Clinical Pharmacology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland

KEY WORDS: extrapolation, efficacy, pediatric drug-development programs

Pediatrics, 2011; 128: e1242-e1249
### Extrapolation approaches and success in achieving new or expanded paediatric indications

<table>
<thead>
<tr>
<th>Extrapolation of efficacy from adults</th>
<th>Supportive evidence requested</th>
<th># products for which approach was used</th>
<th>New or expanded paediatric indication achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>No extrapolation</td>
<td>2 adequate well-controlled efficacy and safety trials plus PK data. Start with Ph I/II in sequential approach. Only proceed if evidence of response. (Oncology products)</td>
<td>19/166 (11%)</td>
<td>7/19 (37%)</td>
</tr>
<tr>
<td>Partial extrapolation</td>
<td>Single adequate well-controlled efficacy and safety trial plus PK data. Single controlled or uncontrolled efficacy and safety trial (qualitative data) plus PK data. Single exposure-response trial (not powered for efficacy) plus PK and safety data. PK/PD and uncontrolled efficacy data plus safety data. PK/PD data plus safety data.</td>
<td>67/166 (40%)</td>
<td>35/67 (52%)</td>
</tr>
<tr>
<td>Complete extrapolation</td>
<td>Pharmacokinetic and safety data. Safety data only</td>
<td>10/166 (6%)</td>
<td>9/10 (90%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14/166 (8%)</td>
<td>6/14 (43%)</td>
</tr>
</tbody>
</table>

**Courtesy of J. Dunne**
Vision: M&S platform for extrapolation

- **Decision making** (quantitative basis for extrapolation)
- **Planning** (Hypothesis generating and study Optimisation)
- **Descriptive and Inferential data analysis** (e.g. POP-PK model to draw conclusions on the PK in children based on sparse sampling)
- **Data synthesis from different sources** (e.g. PBPK to draw conclusion on the PK in children based only on limited PK data in children)
- **Evaluating uncertainties and risks** (e.g. simulate impact of parameters uncertainty, or different what if scenarios where assumptions are violated)
How to interact with EMA

- Scientific Advice/Protocol Assistance (Paediatric Fee waiver)
- Presubmission meetings with paediatric sector
- Discussions during the PIP procedure
- Qualification Advice/Qualification Opinion
- Briefing Meetings with EMA Innovation Task Force (ITF)
Qualification Procedures

**CHMP Qualification Advice** on future protocols and methods for further method development towards qualification

**CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data

**Who can apply?** Consortia, Networks, Public / Private partnerships, Learned societies, Pharmaceutical industry
Extrapolation concept

B. Quantitative evidence

![Graph showing primary efficacy endpoint comparison between source and target populations. The graph indicates a higher efficacy for the target population compared to the source population.](image-url)
Extrapolation concept

B. Quantitative evidence

![Graph showing primary efficacy endpoint comparison between source and target populations. The graph compares the effect size of no/standard treatment versus new treatment, using indicators such as Δ means, RR, OR, HR, and RD.]
Examples
Treatment of acute venous thromboembolism

A. Biological/ pharmacological rationale

- Different underlying diseases and triggers in children vs adults
- Common pathophysiologic pathway: thrombotic vessel occlusion, embolism
- Anticoagulant mechanism: inhibition/reduction of clotting factors – quantitatively different in young infants
- Primary efficacy endpoint: recurrent VTE
- Primary safety endpoint: major bleeding
Treatment of acute venous thromboembolism

B. Quantitative evidence

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>UFH (+VKA)</th>
<th>LMWH (+VKA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong> 0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI 0.55-0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OR</strong> 0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI 0.05-4.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- adults n=8122
- children n=76

Van Dongen, Cochr datab SR 2004
Massicotte, Thromb Res 2003
Treatment of acute venous thromboembolism

B. Quantitative evidence

**Efficacy**
- UFH (+VKA) vs LMWH (+VKA)
  - Adults: OR 0.68 (95%CI 0.55-0.84)
  - Children: OR 0.53 (95%CI 0.05-4.0)

**Safety**
- UFH (+VKA) vs LMWH (+VKA)
  - Adults: OR 0.58 (95%CI 0.39-0.85)
  - Children: OR 0.41 (95%CI 0.07-2.3)

Van Dongen, Cochr datab SR 2004
Massicotte, Thromb Res 2003
Treatment of acute venous thromboembolism

B. Quantitative evidence

**Efficacy**
- **UFH (+VKA)**
- **LMWH (+VKA)**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH (+VKA)</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>LMWH (+VKA)</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>

- OR 0.68 (95%CI 0.55-0.84)
- OR 0.53 (95%CI 0.05-4.0)

**Safety**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH (+VKA)</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>LMWH (+VKA)</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>

- OR 0.58 (95%CI 0.39-0.85)
- OR 0.41 (95%CI 0.07-2.3)

C. Hypothesis

**Recurrent thrombosis (%)**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH (+VKA)</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>New oral anticoagulant</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>

- HR 0.68 (95%CI 0.44-1.04)

**Major bleeding (%)**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH (+VKA)</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
<tr>
<td>New oral anticoagulant</td>
<td>[Graph]</td>
<td>[Graph]</td>
</tr>
</tbody>
</table>

- HR 0.62 (95%CI 0.33-1.3)

**References**
- Van Dongen, Cochr datab SR 2004
- Massicotte, Thromb Res 2003
- NEJM 2010
Partial extrapolation:

Agreed PI P for new oral anticoagulant:

- Paediatric formulation; Bioequivalence study
- PBPK-model; In-vitro concentration-response study
- I: Single dose PK/PD, safety
- II: PK/PD, safety, active-controlled, 4 wks VTE treatment
- III: Efficacy, safety, active-controlled, 3 mo VTE treatment, arbitrary sample size n=150

(studies ongoing)
Hypertension

Conceptual framework modellisation

Jadhav P et al. 2009. Leveraging prior quantitative knowledge in guiding pediatric drug development: a case study
A Bayesian approach to randomized controlled trials in children utilizing information from adults: the case of Guillain-Barré syndrome

Steven N Goodman\textsuperscript{a} and John T Sladky\textsuperscript{b}

- Treatment of GBS: plasmapheresis vs IV immunglobuline
- Efficacy endpoint: time to independent walking
- Bayesian methods to incorporate prior information from adults
- For design of randomized non-inferiority trial in children
  - Significant reduction in sample size (n=160 vs n=750)
Extrapolation framework

Basic consideration:
- similarity of disease / progression
- similarity of response to treatment

1. Extrapolation concept
   Quantitative data synthesis, model building
   Hypothesis

2. Extrapolation plan
   Reduction of data requirements

3. Validation

Adapting → Learning