Considerations for Implementing the EMA Extrapolation Approach: A Global Drug Developer's Perspective

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- EMA invited pharmaceuticals companies including Novartis Pharma AG to participate in an Extrapolation Workshop (held on 17 & 18 May 2016) called to obtain drug developers perspectives on the recently released EMA Extrapolation Reflection Paper.
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Discussion Topics

TOPIC 1

Agreeing on a Paediatric Investigation Plan (PIP) versus agreeing on a pediatric program that can achieve marketing authorization

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Aims of Regulation (EC) No 1901/2006

Recital 4

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EMA Reflection Paper on Extrapolation of Efficacy and Safety in Paediatric Medicine Development

1. Executive summary

This reflection paper proposes a framework for extrapolation of data from adults to children which could serve as a basis for regulatory decision making for Paediatric Investigation Plans. Extrapolation for paediatric medicines development is discussed as a model situation but the underlying principles may be extended to other areas of medicine development.

It is acknowledged that development of a medicine in adults provides a rich source of data to inform paediatric development and given reasonable similarity between adults and children, extrapolation from adults (source population) may reduce paediatric data requirements to make conclusions for use of the medicine in children (target population). This reduction in requirements is of benefit, for ethical reasons as it may minimize exposure of children to studies and because the available paediatric population for study may be limited in number. Therefore, the use of information from adults and other sources should be maximized. Additionally extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources.

The proposed framework provides the basis for an explicit and systematic approach to extrapolation to support paediatric medicine authorisation. The totality of data should allow to:

- conclude on appropriate doses in the various age groups; and
- conclude on efficacy and safety and the benefit-risk balance in the target population.

- "The proposed framework provides the basis for an explicit and systematic approach to extrapolation to support pediatric medicine authorisation."

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"... proposes a framework for extrapolation of data from adults to children which could serve as a basis for regulatory decision making for Paediatric Investigation Plans."

Committees of the EMA

Committee for Medicinal Products for Human Use (CHMP)

- " ... responsible for preparing opinions on questions concerning medicines for human use."

Paediatric Committee (PDCO)

- "... responsible for assessing the content of paediatric investigation plans [PIPs] and adopting opinions on them. This includes assessing applications for full or partial waivers and assessing applications for deferrals."

Regulatory Consideration 1:
To which regulatory body does ‘the’ extrapolation plan and lifecycle maintenance need to be agreed?

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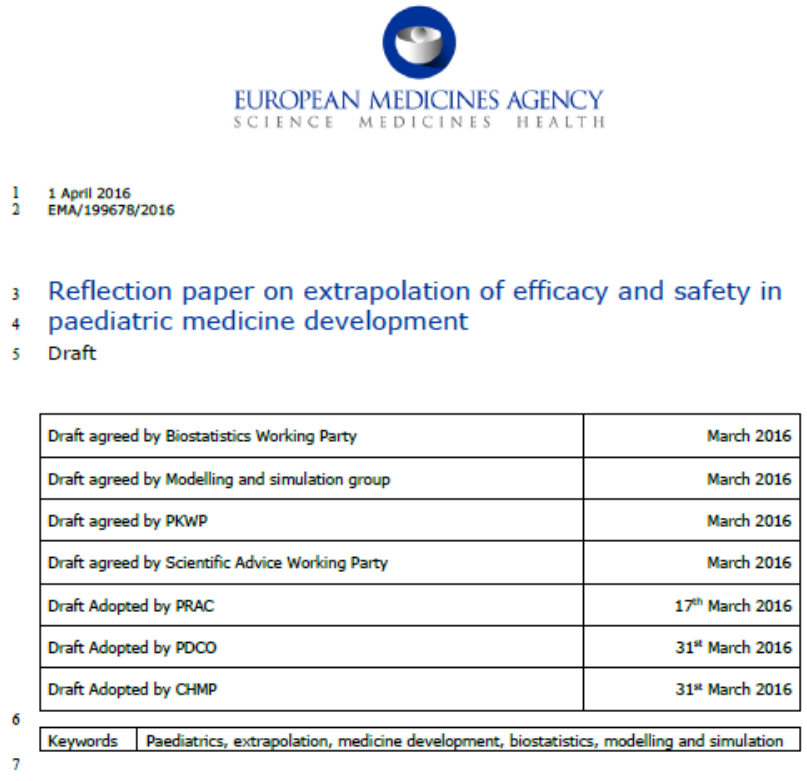

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 April 2016
EMA/199678/2016

Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Draft

Draft agreed by Biostatistics Working Party	March 2016
Draft agreed by Modelling and simulation group	March 2016
Draft agreed by PKWP	March 2016
Draft agreed by Scientific Advice Working Party	March 2016
Draft Adopted by PRAC	17th March 2016
Draft Adopted by PDCO	31st March 2016
Draft Adopted by CHMP	31st March 2016

Keywords	Paediatrics, extrapolation, medicine development, biostatistics, modelling and simulation

- ✓ Paediatric Committee (PDCO)
- ✓ CHMP Standing Working Parties:
  - Scientific Advice Working Party (SAWP)
- ✓ CHMP Temporary Working Parties:
  - Pharmacokinetics Working Party (PKWP)
  - Biostatistics Working Party
- ✓ Other CHMP Groups:
  - Modelling and Simulation Working Group

Additional considerations

- ✓ Within which regulatory body(-ies) does the expertise lie?
  - CHMP and its working parties, PDCO, Both
- ✓ What processes are in place to facilitate an efficient procedure to vet and align on endorsement of an extrapolation plan if more than one body is needed to vet and endorse a plan?
- ✓ Will new joint procedures, stop clocks need to be implemented to facilitate an efficient regulatory pathway?
  - Joint PIP – Scientific Advice procedure

PIP focused

TOPIC 2

Iteration and adaptation as a routine aspect of medicinal product development

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Extrapolation in the product development lifecycle

Section F

F. Extrapolation in the product development life cycle

Consideration should be given to extrapolation at the early planning stages of a development program, since, when pursued, it is expected to impact profoundly on data requirements (in terms of content and timing, both in source and target population) during the course of a product development life cycle. For all the above reasons, applicants are encouraged to discuss extrapolation early on with regulatory authorities. It is indeed anticipated that opportunity for extrapolation, with anticipated benefit of early market access, will be missed when not planned and discussed early.

Extrapolation is expected to be the subject of at least two (and likely more) regulatory interactions:

- early regulatory review of extrapolation concept and plan (at the latest at the expected time of PIP application, but often likely earlier in view of impact on overall development program)
- model validation (by applicant) resulting in (iterative) refinement/correction of model
  - regulatory review of source and target data and of the results of the model validation process. If such a process suggests that the assumption underpinning extrapolation are not correct and could call into question the extrapolation concept, this can lead to:
- refutation (by applicant) of model(s) and extrapolation concept
  - regulatory interaction/PIP modification to propose/request modification of extrapolation program or discontinuation

It is envisaged that such an approach should mean that by the time the extrapolation plan has been agreed, and paediatric development commences, there are likely to be very few changes to studies in the PIP that support the extrapolation concept.

- "Extrapolation is expected to be the subject of at least two (and likely more) regulatory interactions …"

1. Early review
2. Model validation
3. Refutation

- "...by the time the extrapolation plan has been agreed, ..., there are likely to be very few changes to studies in the PIP that support the extrapolation concept."

Timing of PIP submission

Article 16 of the Paediatric Regulation

Article 16

1. In the case of the applications for marketing authorisation referred to in Articles 7 and 8 or the applications for waiver referred to in Articles 11 and 12, the paediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmaco-kinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC, so as to ensure that an opinion on use in the paediatric population of the medicinal product concerned can be given at the time of the assessment of the marketing authorisation or other application concerned.

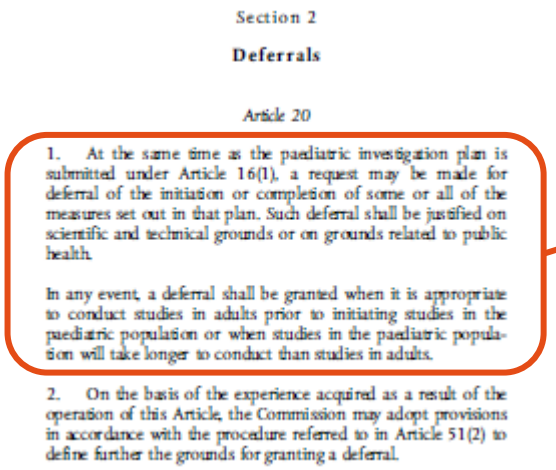
2. Within 30 days following receipt of the request referred to in paragraph 1 and in Article 15(1), the Agency shall verify the validity of the request and prepare a summary report for the Paediatric Committee.

3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until such time as the supplementary information requested has been provided.

- "...shall be submitted ..., except in duly justified cases, not later than upon completion of the human PK studies in adults ...."

Defining a deferral

Article 20 of the Paediatric Regulation



Section 2

Deferrals

Article 20

1. At the same time as the paediatric investigation plan is submitted under Article 16(1), a request may be made for deferral of the initiation or completion of some or all of the measures set out in that plan. Such deferral shall be justified on scientific and technical grounds or on grounds related to public health.

In any event, a deferral shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

2. On the basis of the experience acquired as a result of the operation of this Article, the Commission may adopt provisions in accordance with the procedure referred to in Article 51(2) to define further the grounds for granting a deferral.

- "...a request may be made for deferral of the initiation or completion of some or all of the measures set out in that plan ... justified on scientific or technical grounds ... . shall be granted when ... appropriate to conduct studies in adults prior to initiating studies in the pediatric population ... ."

Regulatory Consideration 2:
The iterative aspects of extrapolation reflects a regulatory need to transition to ‘staged’ agreement on pediatric plans

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Additional considerations

- ‘By-phase’ regulatory agreement is routine for medicinal product development
  - The Regulation does not prohibit this approach
- Extrapolation planning relies on pre-existing information as well as generation of new data
- Iteration and adaptation are a fundamental component of any extrapolation plan
- ✓ How can the Agency utilize the aims of the Extrapolation Reflection Paper to transition pediatric planning from a one-time agreement early in the development lifecycle to more closely resemble actual product development? The so-called ‘two-stage’ PIP?

Additional considerations (2)

- ❖ Consideration of iteration and adaptation should be a fundamental component of any agreed extrapolation plan
- ✓ Under what circumstances would the Agency require a plan to be “re”-discussed for agreement?
- ✓ Within which regulatory body(-ies) does the expertise lie?
  - CHMP and its working parties, PDCO, Both
- ✓ Through what regulatory procedure is a sponsor to seek agreement?

Additional considerations (3)

- Pre-release ICH E-11 (R1) document:

Line 93 Pediatric drug development programs are increasingly global; therefore, efficient
Line 94 development of those products in pediatric patients relies on coordinated efforts that are
Line 95 based on sound scientific content.

- ✓ How is the EMA evaluating the proposed Extrapolation framework to ensure that it does not unwittingly introduce inefficiencies in global regulatory coordination and program execution?

- ✓ What joint global regulatory procedures could be envisaged to ensure sponsors have the opportunity for a more efficient means of seeking alignment of scientific approach?

PIP focused



TOPIC 3

Validation and Confirmation of an extrapolation approach in the context of Compliance with an Agreed PIP and Reward

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The interaction of confirmation and Compliance with an agreed PIP

458 **D.1.Validation / confirmation**

459 As well as potentially answering questions related to efficacy in and of themselves, the data observed
460 in the target population as part of the extrapolation plan should be used to validate the extrapolation
461 concept, specifically to validate the modelling approaches and assumptions used for extrapolation, and
462 to confirm the PK and PD predictions, the predicted degree of differences (or understanding) in disease
463 progression, and in clinical response.

464 The consistency between the predictions in the extrapolation concept and the observed data should be
465 confirmed, ensuring that any substantial deviation from the predictions is ruled out. In most settings, a
466 true validation of the assumption might not be possible but methods should be used that are
467 responsive to relevant deviations from the assumptions.

468 If the data do not confirm the extrapolation concept, i.e. larger observed than predicted differences
469 between source and target population, the extrapolation concept needs to be updated accordingly and,
470 hence, the ability to extrapolate. Consequently, the need to generate more data in the target
471 population should be assessed and the extrapolation plan adjusted.

472 This may be an iterative process of predicting and confirming, or adapting, when moving through the
473 phases of clinical development, and from one age-group to the next. Adjustments may even be made
474 during an individual trial using an adaptive design – for example choosing the optimal dose based on
475 PK/PD confirmation early in the trial, and dropping those doses not considered optimal, while
476 continuing to randomise patients.

477 When it has already been established in a specific therapeutic area guideline that extrapolation is
478 possible, further data to validate the extrapolation concept may not be necessary

- "If the data do not confirm an extrapolation concept ... the extrapolation concept needs to be updated accordingly... . Consequently, the need to generate more data in the target population should be assessed and the extrapolation plan adjusted."

Compliance with an agreed PIP

Article 23 of the Paediatric Regulation

Section 4

Compliance with the paediatric investigation plan

Article 23

1. The competent authority responsible for granting marketing authorisation shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Articles 7 and 8 and whether an application submitted pursuant to Article 30 complies with the agreed paediatric investigation plan.

Where the application is submitted in accordance with the procedure set out in Articles 27 to 39 of Directive 2001/83/EC, the verification of compliance, including, as appropriate, requesting an opinion of the Paediatric Committee in accordance with paragraph 2(b) and (c) of this Article, shall be conducted by the reference Member State.

2. The Paediatric Committee may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan:

(a) by the applicant, prior to submitting an application for marketing authorisation or variation as referred to in Articles 7, 8 and 30, respectively;

(b) by the Agency, or the national competent authority, when validating an application, as referred to in point (a), which does not include an opinion concerning compliance adopted following a request under point (a);

(c) by the Committee for Medicinal Products for Human Use, or the national competent authority, when assessing an application, as referred to in point (a), where there is doubt concerning compliance and an opinion has not been already given following a request under points (a) or (b).

In the case of point (a), the applicant shall not submit its application until the Paediatric Committee has adopted its opinion, and a copy thereof shall be annexed to the application.

3. If the Paediatric Committee is requested to give an opinion under paragraph 2, it shall do so within 60 days of receiving the request.

Member States shall take account of such an opinion.

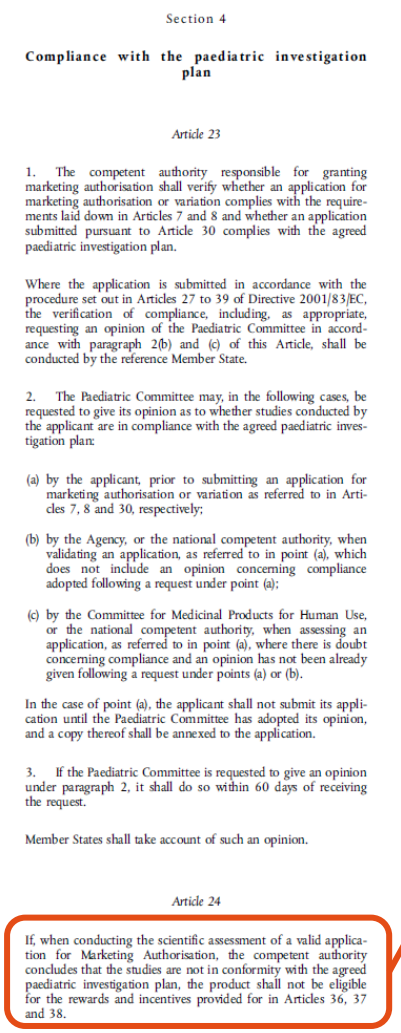
Article 24

If, when conducting the scientific assessment of a valid application for Marketing Authorisation, the competent authority concludes that the studies are not in conformity with the agreed paediatric investigation plan, the product shall not be eligible for the rewards and incentives provided for in Articles 36, 37 and 38.

- "The competent authority responsible for granting MA shall verify whether an application for MA or variation complies with ... the agreed PIP."

The interaction of Compliance and Reward

Article 24 of the Paediatric Regulation (as well as Title V)



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- "If assessing the scientific assessment of a valid application for MA, ... studies are not in conformity with the agreed PIP, the product shall not be eligible for the rewards and incentives ... ."

PIP focused

Regulatory Consideration 3:
How does the Reflection Paper mitigate/ introduce uncertainty for sponsors in relation to securing compliance check and opportunity for Reward?

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Additional considerations

- Data generated from studies that were detailed in an agreed PIP may not confirm an extrapolation concept (even after the measures have been completed as agreed)

- ✓ In this scenario, can the Agency envisage pathways whereby sponsors would not be allowed to seek compliance check? Reward?
- ✓ Can the Agency envisage a pathway whereby completed PIPs with “failed” extrapolation concepts can propose a revised extrapolation plan to be completed as a FUM as opposed to being required to Modify the PIP?
- ✓ Does a completed PIP with a “failed” extrapolation concept negate the possibility for a sponsor to secure Reward?

In Summary

- The Extrapolation Reflection Paper is a welcome tool to assist in advancing pediatric medicinal product development

- To successfully implement the vision EMA has for companies to consider an Extrapolation approach, careful consideration is needed in relation to:

  1. Whom an extrapolation plan and its lifecycle maintenance should be agreed
  2. How the iterative nature of extrapolation may better reflect a need for ‘staged’ agreement on pediatric plans
  3. How failed validation and confirmation may introduce uncertainty for sponsors in relation to securing compliance check and opportunity for Reward

Thank You!

Questions?

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With credits to
Denis Burkhalter
Genevieve Le Visage
Pauline Roudot
Oliver Sander

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