EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Extrapolation in inflammatory bowel disease

EMA Expert Workshop on IBD

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Declaration of conflict of interest

No interest to declare.

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Paediatric Regulation

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use

TITLE I

INTRODUCTORY PROVISIONS

CHAPTER 1

Subject matter and definitions

Article 1

This Regulation lays down rules concerning the development of medicinal products for human use in order to meet the specific therapeutic needs of the paediatric population, without subjecting the paediatric population to unnecessary clinical or other trials and in compliance with Directive 2001/20/EC.

Extrapolation **definition**

(EMA Extrapolation CP)

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 minimising the need to generate additional information (types of studies, number of patients required)

to reach conclusions for the target population.

Use of extrapolation

- in clinical practice
- in clinical trials
- during authorisation
- in quality of biologics
- in biosimilarity evaluation

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- in clinical practice
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- during authorisation
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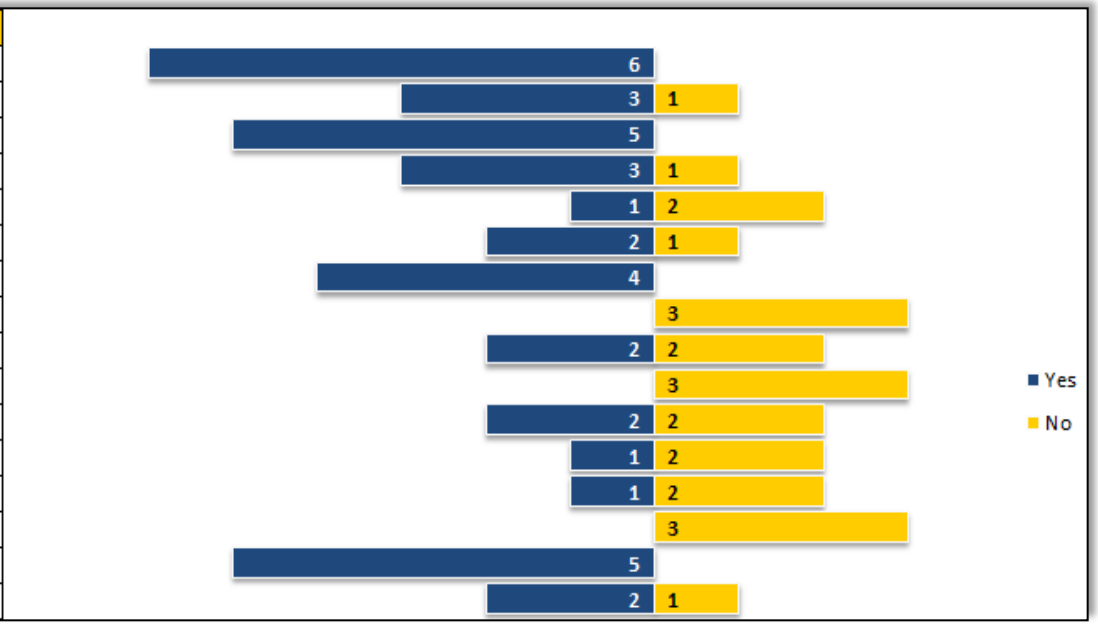
- sound scientific principles
- totality of the evidence
- in case of doubt, additional (non)clinical data
- management of uncertainty

Validation of extrapolation

What is necessary for your decision

to use in practice (on or off label) the novel treatment for UC/CD in children?

Description	Yes	No
change in clinical index in adults	6	0
change in clinical index in children	3	1
change in patient's well-being in adults	5	0
change in patient's well-being in children	3	1
change in PRO in adults	1	2
change in PRO in children	2	1
change in endoscopy findings in adults	4	0
change in endoscopy findings in children	0	3
change in histology findings in adults	2	2
change in histology findings in children	0	3
change in serological marker(s) in adults	2	2
change in serological marker(s) in children	1	2
change in radiographic/MR image in adults	1	2
change in radiographic/MR image in children	0	3
safety in adults	5	0
safety in children	2	1



What change compared to placebo or active comparator would be in your opinion necessary for authorisation of a paediatric indication?

Description	Yes	No
change in clinical index in adults	5	0
change in clinical index in children	4	0
change in patient's well-being in adults	3	1
change in patient's well-being in children	4	0
change in PRO in adults	2	2
change in PRO in children	3	2
change in endoscopy findings in adults	5	0
change in endoscopy findings in children	4	1
change in histology findings in adults	2	2
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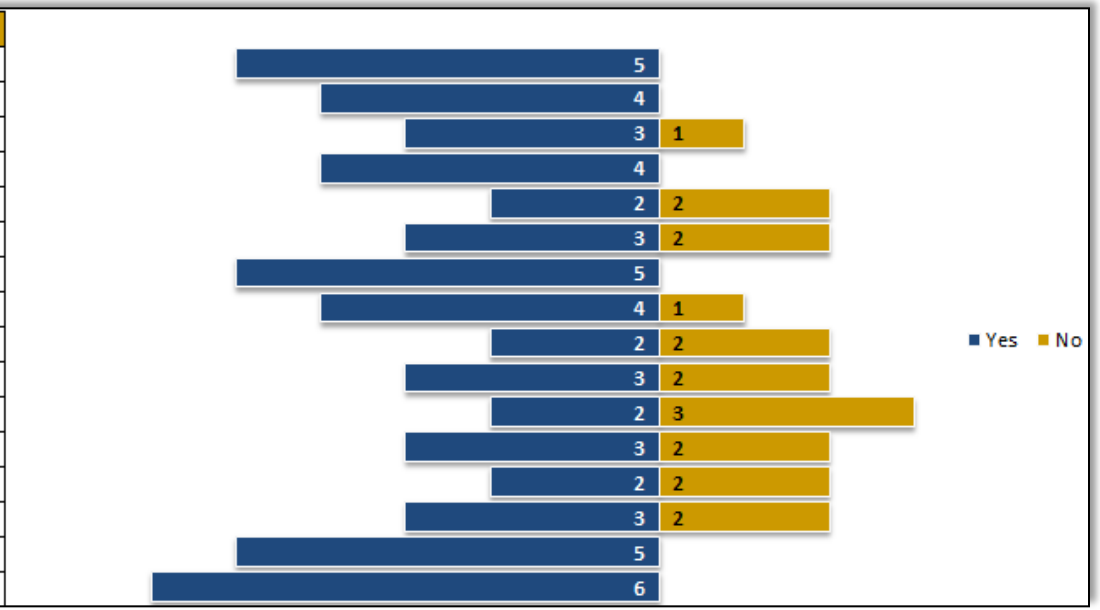
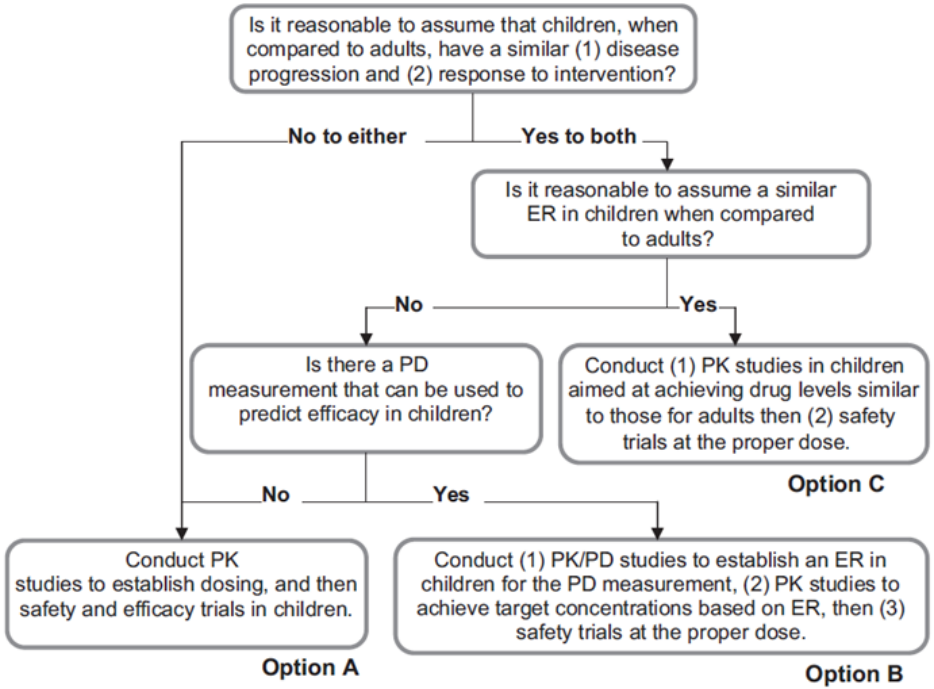
change in serological marker(s) in adults	2	3
change in serological marker(s) in children	3	2
change in radiographic/MR image in adults	2	2
change in radiographic/MR image in children	3	2
safety in adults	5	0
safety in children	6	0



FDA approach to extrapolation (proposed 1994)



Overview of on-going extrapolation activities

- EMA Extrapolation Group
- Extrapolation Concept Paper (2012)
- Handling of extrapolation in paediatric development
- EMA experts workshop September 2015
- EMA industry workshop April 2016 (TBC)
- EMA Extrapolation Reflection Paper
- ICH E11 Revision1
- ICH Concept Paper on Paediatric Extrapolation

Extrapolation **Concept paper**

19 March 2013
EMA/129698/2012
Human Medicines Development and Evaluation

Concept paper on extrapolation of efficacy and safety in medicine development

Final

Agreed by Scientific Advice Working Party	25 April 2012
Agreed by Biostatistic Working Party	15 May 2012
Agreed by PK Working Party	30 May 2012
Agreed by COMP	10 May 2012
Adoption by PDCO	16 May 2012
Adoption by CHMP	24 May 2012
Start of public consultation	29 June 2012
End of consultation (deadline for comments)	30 September 2012

Extrapolation Reflection paper – work in progress

- Focus on the extrapolation between age groups
- Adding **quantitative** approach to the extrapolation concept

  - How to weigh the strength of prior information?
  - How to define and quantify similarity of disease (progression), of PK/PD, of clinical response to treatment and safety aspects
  - Use of statistical modelling

1. Extrapolation **concept**:

A. Biological / pharmacological rationale

- similarity of disease
- drug disposition & effect
- applicability of clinical endpoints

B. Quantitative evidence

- modelling and simulation
- PK/PD

C. Hypothesis (‚model‘)

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

2. Extrapolation **plan**:

Generate a set of rules and methodological tools for the **reduction of data requirements 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 are expected

3. **Validation**:

Use of **emerging data** to validate

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

Revisit assumptions and refine EP concept and plan

Quantitative approach

- Need to further develop algorithm(s) linking degree of similarity with reduction in data requirement
- How to quantify the uncertainty of extrapolation assumptions?
- How to validate assumptions in the extrapolation concept?
- How to analyse and report post-authorisation data to support extrapolation?

Extrapolation in JIA – possible approach

- It is reasonable to assume that RA and JIA are sufficiently similar diseases with similar response to treatment
- PD measurement is similar (ACR, DAS)
- ER in JIA may be similar to RA but PK/PD may be different in children
- Option B or Option C of the FDA algorithm apply.

No efficacy studies needed?

Centrally authorised medicinal products for pJIA

- **ENBREL (entanercept) –** EMEA/H/C/000262 **– 2000**
- **HUMIRA (adalimumab) -** EMEA/H/C/000481/II/0039 **– 2008**
- **ORENCIA (abatacept) –** EMEA/H/C/000701/II/0024 **– 2010**
- **ROACTEMRA (tocilizumab) –** EMEA/H/C/000955/II/0026 **– 2013**

Paediatric studies – Results

Endpoint in Part I: % of patients with JIA ACR30 response

Part I	**% of patients with JIA ACR30 response**		duration of Part I
Enbrel	74%	51/69	13 weeks
Humira	84%	144/171	16 weeks
Orencia	65%	123/190	16 weeks
RoActemra	89%	168/188	16 weeks

Endpoint in Part II: % of patients with disease flare based on JIA ACR30 criteria

Part II	**% of patients with disease flare**						
	act. subs.		**placebo**		p value	N of patients	duration of Part II
Enbrel	24%	6/25	77%	20/26	0.0002	51	16 weeks
Humira	40%	27/68	68%	44/65	0.0017	133	32 weeks
Orencia	20%	12/60	53%	32/62	0.0003	122	24 weeks
RoActemra	26%	21/82	48%	39/81	0.0035	163	24 weeks

ROACTEMRA (tocilizumab) – Paediatric dose development

ADULTS	•extrapolation was not envisaged as given by PIP → more comprehensive clinical development was employed •adult dose 8 mg/kg applied in small supportive paediatric studies
CHILDREN Small supportive study	•dose 8 mg/kg applied in Japanese MRA318JP study (19 subjects, 12 weeks)
Dose Calculation	•PK model (two-compartment) created and a higher dose (10 mg/kg) was suggested for children weighing < 30 kg
CHILDREN Pivotal study	•≥ 30 kg → 8 mg/kg •< 30 kg → 10 mg/kg **OR** 8 mg/kg for < 30 kg •Another PK model created (two-compartment) → efficacy results and PK model confirmed the choice of doses, that were later approved: 8 mg/kg for ≥ 30kg, 10 mg/kg for < 30 kg

Summary

- RA and JIA are clinically sufficiently similar and use similar endpoints for evaluation of efficacy
- Extrapolation (at least “partial”; although not specifically discussed) in pJIA has been commonly used in previous MA procedures in JIA (randomised withdrawal studies in limited number of patients)

  WHAT ABOUT INFLIXIMAB AND GOLIMUMAB?!
- However, there is no standardised approach/methodology
- Need for quantitative analysis
- Disease progression, PK and PD, and clinical response can be quantified - **how to perform this quantification?**
- Need for PK/PD studies to determine the best paediatric dose (see RoActemra)

Extrapolation in IBD

Is it possible to extrapolate in ulcerative colitis and Crohn's disease from adults to children?

- Efficacy
- Safety
- Dose

Is the disease (UC and CD) sufficiently similar in adults and children to expect the similar treatment effect in adults and children? If yes, what studies are needed in children for medicines that are authorised in adults?

Yes!

(according to survey)

What to quantify?

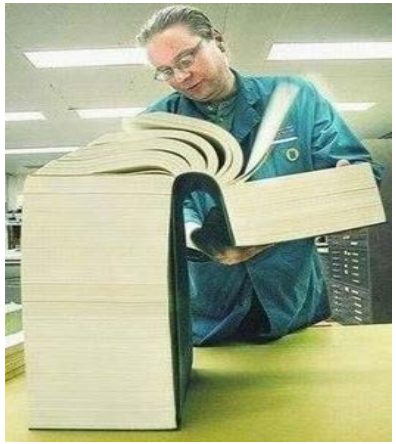
- Similarity of target exposure
- Dose/exposure similarity
- Are there differences as for age groups?
- Need for different exposure in paediatric age groups?
  - Safety
  - Efficacy
  - Benefit/risk

Modelling approach/data analysis

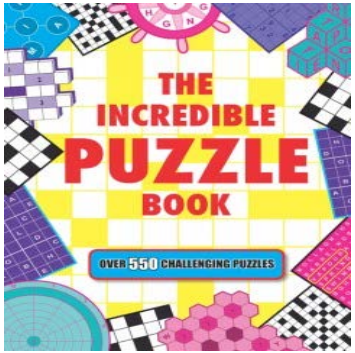
- **All available data** should be used;
  - also failures important to include
  - investigate causes of failure - exposure, placebo response, study design…
- Comparison of **D-E relationship**
  - for adults to children
  - comparison across substances
- Comparison of **E-R relationship**
  - across substances
  - across (sub)populations
- **Joint modeling** (or statistical analysis) of all substances
  - to check consistency of PD-response
  - to check consistency of placebo response/active comparator effects between populations?
  - to investigate impact of study design (clinical trial simulations)
- Retrospective **analysis of power** (also how an analysis with borrowed power from the adult data would have looked)

Is extrapolation possible in new class?

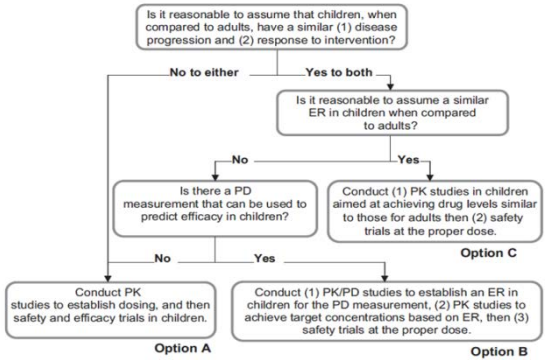
Naturally amount of available data is different between established class of medicines (e.g. anti-TNFs)



and new molecule with novel mechanism of action!



What is “necessary”?



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Extrapolation is necessary (as 1st step!)

- To avoid unnecessary trials in children
- To secure early access to safe and effective treatment for children
- To allow feasibility of paediatric development

- Extrapolation is not a new concept
- Using scientifically robust extrapolation and validation of extrapolation method

- this is necessary!

Thank you for your attention

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Further information

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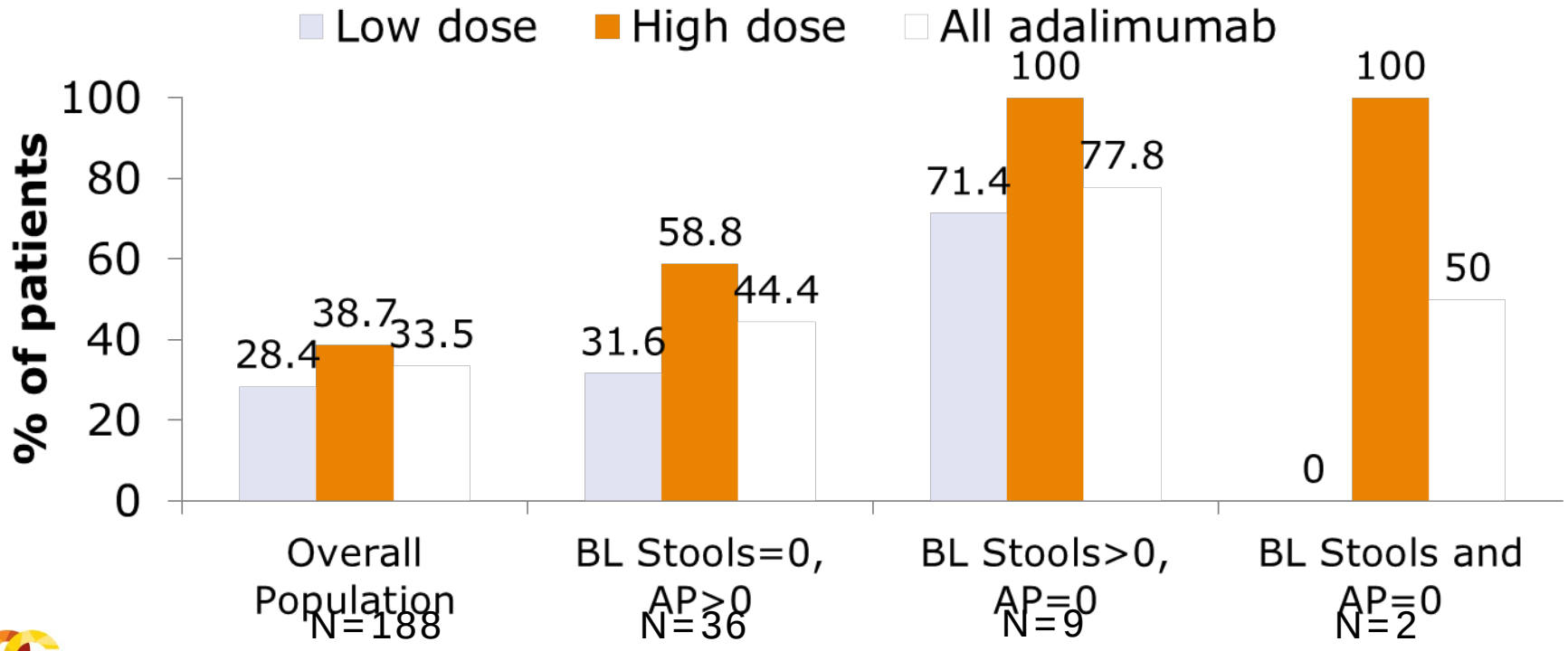
Remission (PCDAI ≤ 10) at Week 26



Non-responder imputation for missing data or patients who escaped to OL therapy.
Low dose: adalimumab 20/10 mg; high dose: adalimumab 40/20 mg.