Extrapolation in Pediatric Product Development:

Practical Application of the Principle of Scientific Necessity

Robert 'Skip' Nelson, MD PhD
Deputy Director and Senior Pediatric Ethicist
Office of Pediatric Therapeutics, Office of the Commissioner
Food and Drug Administration, Silver Spring MD
<Robert.Nelson@fda.hhs.gov>

Disclaimer

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- Robert Nelson has no financial conflicts of interest to disclose.

Ethical Principle of Scientific Necessity (Practical Application: Extrapolation)

- Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children
  - Practical application (using extrapolation): determine the type (and timing) of clinical studies required to establish "safe and effective" pediatric use of drugs or devices
- Derives from requirements for equitable selection[†]
  - Subjects capable of informed consent (i.e., adults) should generally be enrolled prior to children

[†] Minimize Risks and Equitable Selection [US 21 CFR 56.111(a)(1) and (b)]

Extrapolation

- Generally understood, extrapolation is an inference from the known to the unknown.
  - to use known facts as the starting point from which to draw inferences or conclusions about something unknown
  - to predict by projecting past experience or known data
- Extrapolation of pediatric efficacy has a specific legal definition.
  - "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." (21 CFR §355c)
- A powerful tool to be used carefully.

Use of Extrapolation

- The use of extrapolation was first introduced in the 1994 Pediatric Labeling Rule, but did not have much of an impact until the pediatric incentives (BPCA "exclusivity" in 1997, and PREA "requirement" in 2003) were established.
- "A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted."

Substantial Evidence of Effectiveness

- "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved" [1962]
  - Section 505(d), Food, Drug & Cosmetic Act
  - "Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."
- "FDA has been flexible…, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing."
  - In 1997, "Congress amended section 505(d)… to make it clear that [FDA] may consider 'data from one adequate and well-controlled clinical investigation and confirmatory evidence' to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness."
  - In doing so, "Congress confirmed FDA's interpretation of the statutory requirements for approval."

Extrapolation from Existing Studies

- "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated *without* additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because *other types of data* provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form." (emphasis added)

For Extrapolation of Effectiveness from Adult to Pediatric Population

- "Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions."

Summary of Approaches to Extrapolation

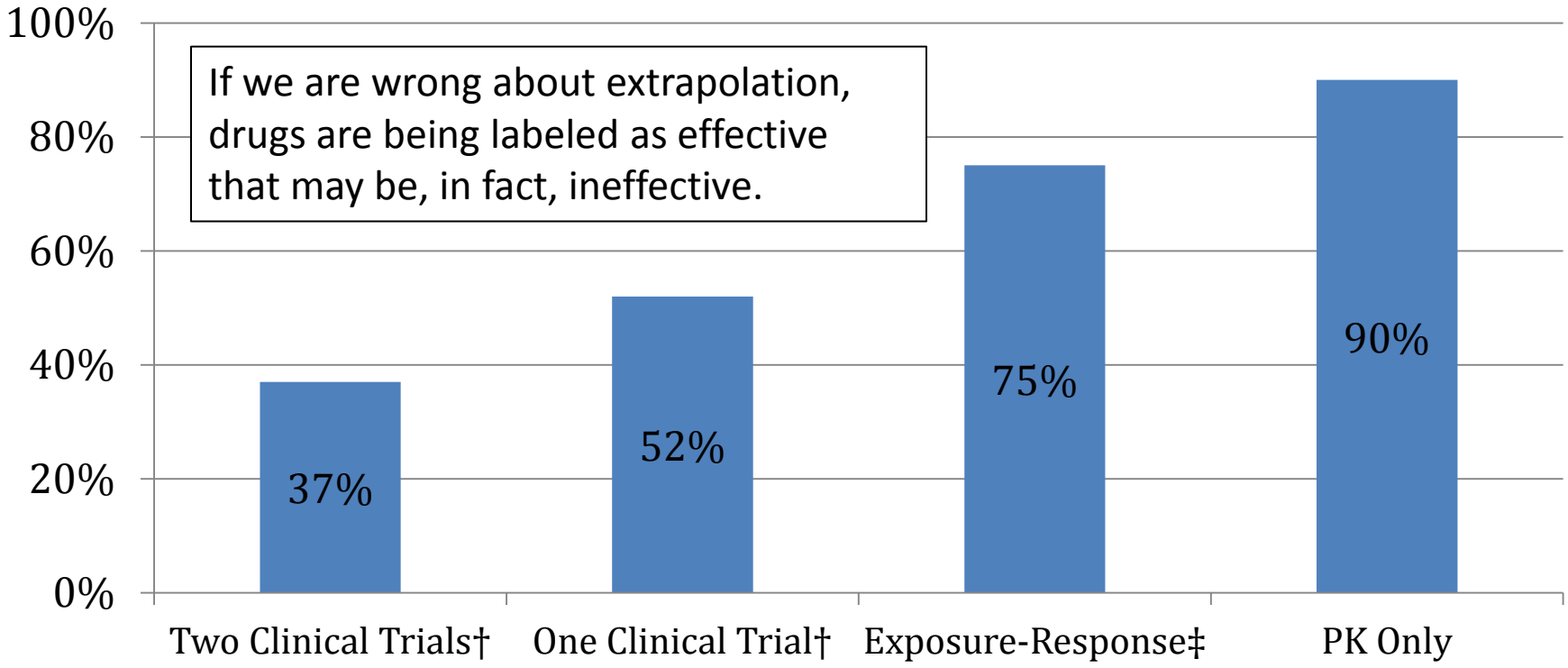
(Assessment of 166 products between 1998-2008)

Extrapolation	Supportive Evidence Requested From Pediatric Studies	Products n/N (%)	New or Expanded Indication
None **17%**	Two adequate, well-controlled, efficacy and safety trials plus PK data.	19/166 (11)	7/19 (37)
	Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial **68%**	Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.	67/166 (40)	35/67 (52)
	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.	20/166 (12)	15/20 (75)
	Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.	26/166 (16)	19/26 (73)
Complete **14%**	PK and safety data.	10/166 (6)	9/10 (90)
	Safety data only.	14/166 (8)	6/14 (43)

Adapted from Table 1: Dunne J et al. Pediatrics 2011;128;e1242.

New or Expanded Indication

A powerful tool to be used carefully!

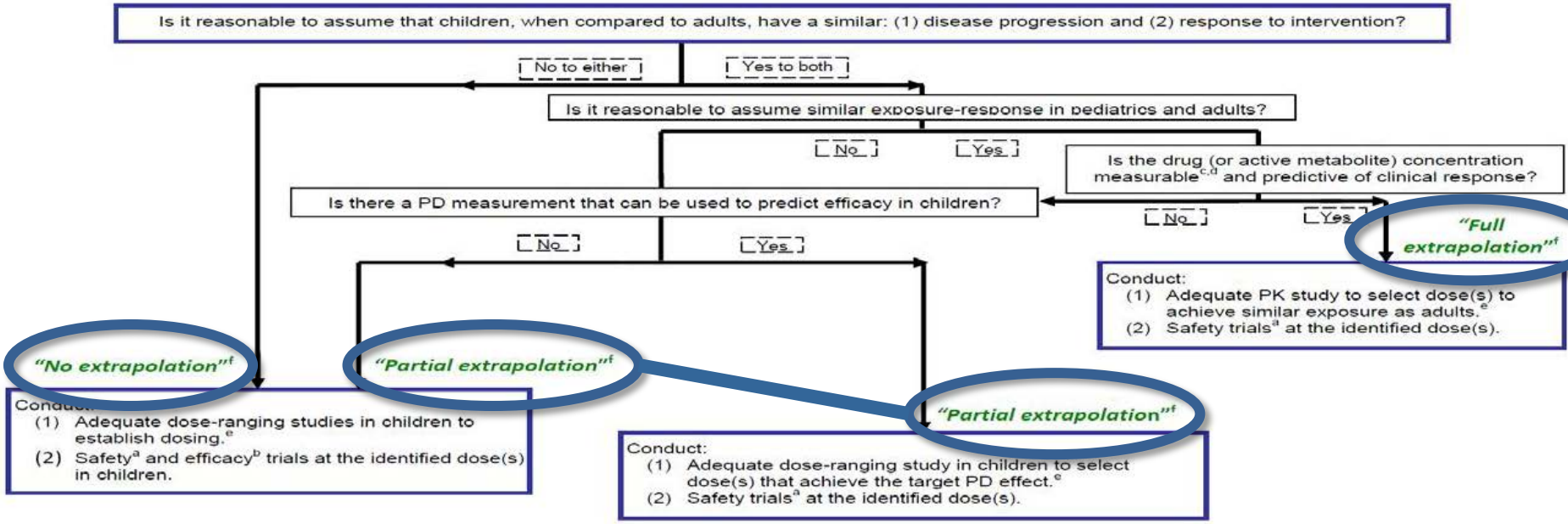


† Adequate, well-controlled, efficacy and safety trial(s) (powered for efficacy), plus PK data.

‡ Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data; or single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.

Adapted from Table 1: Dunne J et al. Pediatrics 2011;128;e1242.

Pediatric Study Planning & Extrapolation Algorithm



Footnotes:

a. For locally active drugs, includes plasma PK at the identified dose(s) as part of safety assessment.
b. For partial extrapolation, one efficacy trial may be sufficient.
c. For drugs that are systemically active, the relevant measure is systemic concentration.
d. For drugs that are locally active (e.g., intra-luminal or mucosal site of action), the relevant measure is systemic concentration only if it can be reasonably assumed that systemic concentrations are a reflection of the concentrations at the relevant biospace (e.g., skin, intestinal mucosa, nasal passages, lung).
e. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.
f. For a discussion of no, partial and full extrapolation, see Dunne J, Rodriguez WJ, Murphy MD, et al. "Extrapolation of adult data and other data in pediatric drug-development programs." Pediatrics. 2011 Nov;128(5):e1242-9.

No Extrapolation

Is it reasonable to assume that children, when compared to adults, have a similar (1) disease progression and (2) response to intervention?

Also applies to extrapolation between definable pediatric subpopulations

either

Conduct:

(1) Adequate dose-ranging studies in children to establish dosing.[a]

(2) Safety[b] and efficacy trials at the identified dose(s) in children.

Refer to May 1998 FDA Guidance on substantial evidence of efficacy

Footnotes:

a. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.

b. For locally active drugs, includes plasma PK at the identified dose(s) as part of the safety assessment.

Full Extrapolation

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

↓ Yes to Both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

↓ Yes

Is drug (or active metabolite) concentration measureable & predictive of clinical response?

↓ Yes

Conduct:

(1) Adequate PK study to select dose(s) to achieve similar exposure as adults.[a]

(2) Safety[b] trials at the identified dose(s) in children.

Footnotes:

a. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.

b. For locally active drugs, includes plasma PK at the identified dose(s) as part of the safety assessment.

Partial Extrapolation

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

Yes to Both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

No

Is there a PD measurement that can be used to predict efficacy in children?

No

Continued on next slide.

Yes

Continued on next slide.

Partial Extrapolation (cont.)

Is it reasonable to assume similar exposure-response in pediatrics and adults?

No

Is there a PD measurement that can be used to predict efficacy in children?

No

Conduct:

(1) Adequate dose-ranging studies in children to establish dosing.[a]

(2) Safety[b] and efficacy[c] trials at the identified dose(s) in children.

Yes

Conduct:

(1) Adequate dose-ranging study in children to select dose(s) that achieve the target PD effect.[d]

(2) Safety[b] trials at the identified dose(s).

Footnotes:

a. When appropriate, use of modeling and simulation for dose selection (supplemented by pediatric clinical data when necessary) and/or trial simulation is recommended.

b. For locally active drugs, includes plasma PK at the identified dose(s) as part of the safety assessment.

c. For partial extrapolation, one efficacy trial may be sufficient.

d. For drugs that are systemically active, the relevant measure is systemic concentration.

EMA Definition of Extrapolation

- "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*." (emphasis added)

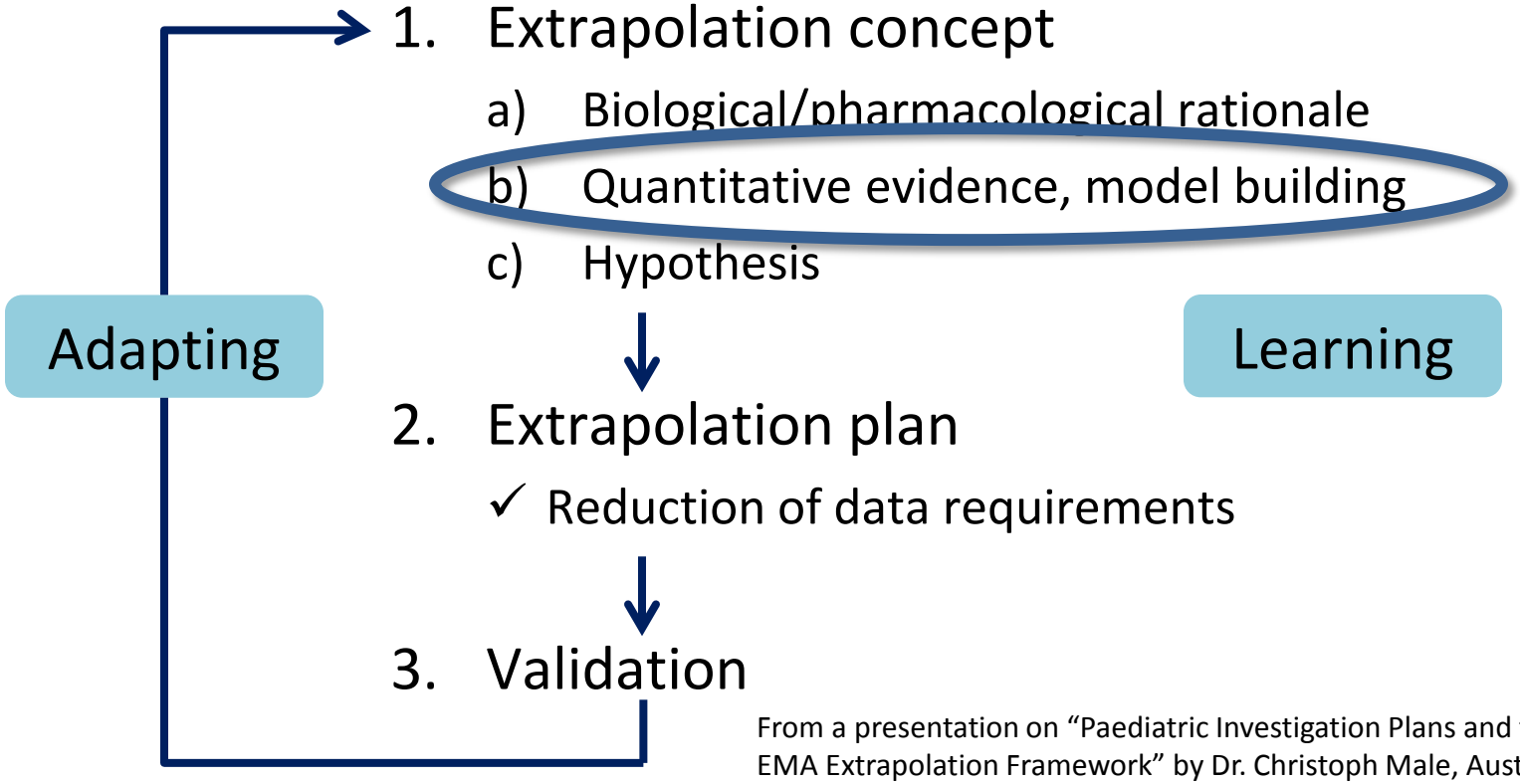
Areas of extrapolation

- "Extrapolation from adults to children is a typical example *but extrapolation may be applied in many other areas*: e.g. i) between population subsets,…; 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." (emphasis added)

Extrapolation Framework

Stepwise Approach

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



From a presentation on "Paediatric Investigation Plans and the EMA Extrapolation Framework" by Dr. Christoph Male, Austrian Delegate to the EMA Paediatric Committee (PDCO) , delivered to the June 2013 GRiP Workshop held in Glascow, Scotland, UK.

Extrapolation Concept

A. Biological/pharmacological rationale

- Similarity of disease
  - ✓ Etiology, pathophysiology
  - ✓ Clinical manifestation
  - ✓ Course, progression (indicators)
- Similarity of drug disposition and effect
  - ✓ Mode of action
  - ✓ PK
  - ✓ PD
- Similarity and applicability of clinical endpoints
  - ✓ Efficacy
  - ✓ Some safety aspects

From a presentation on "Paediatric Investigation Plans and the EMA Extrapolation Framework" by Dr. Christoph Male, Austrian Delegate to the EMA Paediatric Committee (PDCO) , delivered to the June 2013 GRiP Workshop held in Glascow, Scotland, UK.

Extrapolation Concept

B. Quantitative evidence, model building

- Disease models could be used to characterize the differences in disease progression between groups
- Existing data and physiology-based PK/PD modelling and simulation could be used to investigate relationship between PK/PD, body size, maturation, age and other important covariates (e.g., age, renal and hepatic function)
- Quantitative synthesis/modelling of all relevant data (in-vitro, preclinical, clinical and literature) could be used to predict similarity in clinical response (efficacy, some safety aspects) between source and target population

C. Hypothesis/Model

- Explicit (quantitative) statement on the expected differences in response to the drug between target and source population (with assumptions and uncertainties to be specified)

Adapted from a presentation on "Paediatric Investigation Plans and the EMA Extrapolation Framework" by Dr. Christoph Male, Austrian Delegate to the EMA Paediatric Committee (PDCO) , delivered to the June 2013 GRiP Workshop held in Glascow, Scotland, UK.

Extrapolation Plan

Differences between populations	Uncertainty of hypothesis	Extrapolation	Study program (target population)
Large	High	No extrapolation	Full development program
Moderate	Some	Partial extrapolation	Reduced study program dependent on magnitude of expected differences and/or degree of uncertainty
Small	Low	Full extrapolation	Some supportive data for validation

- ✓ Generate rules/methodological tools for reducing data requirements (types of studies, design modifications, number of patients) based on expected degree of similarity; validate extrapolation concept, complement data extrapolated from source populations(s), focus on areas where largest differences expected

Adapted from a presentation on "Paediatric Investigation Plans and the EMA Extrapolation Framework" by Dr. Christoph Male, Austrian Delegate to the EMA Paediatric Committee (PDCO) , delivered to the June 2013 GRiP Workshop held in Glascow, Scotland, UK.

Thank you.