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SCIENCE MEDICINES HEALTH

ACT EU Multi-Stakeholder Workshop on Methodology Guidance: A patient-centred approach to methodologies

Breakout session B: Paediatric clinical trials

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An agency of the European Union

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees.

Drug development takes place in an ecosystem

- Drug development and access to (novel/ essential) involves different stakeholders and decision makers (with different objectives) at different time points.

- Key to identifying barriers within this ecosystem (eg ranging from content, process to capacity)
  - developing solutions (guidance etc) together, educating on the latter to
  - ensuring consistency in implementation, including feedback loop to learn and adapt (in case of 'failure')

- Paediatric specificities to be acknowledged

Paediatric specificities

- Paediatric drug development takes place in the rare disease space, is highly regulated and a global enterprise, with not only the patient but also the parent/caregiver in mind.

- Growing pipelines of innovative products: how to identify and support completion of development efforts in children for products able to address existing unmet medical needs?
  - the need to be innovative, fostering a R&D environment that allows for evolution of scientific knowledge and takes changing evidence and unmet needs into consideration

- Acknowledgment that regulatory decision making on (mandated) paediatric developments cannot take place in isolation.

Actions to support the development of medicines for children

- Increased alignment of data requirements between decision-makers


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6 February 2023
EMA/635567/2022
Paediatric Medicines Office

Boosting the development of medicines for children
Closing report of the European Medicines Agency and European Commission (DG Health and Food Safety) action plan on paediatrics

→ Continues need for (developments of) adequate methodology guidance

4 https://www.ema.europa.eu/en/documents/report/boosting-development-medicines-children-closing-report-european-medicines-agency-european-commission_en.pdf

Use of extrapolation

Need to uniformly understand and apply adequate use of extrapolation across respective decision-making steps within a products life-cycle


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eunethta

06 April 2022
EMA/697891/2021

Priority topics for European collaboration between regulators and health technology assessment bodies

Development of a joint work plan (2021-2023) between EMA and European HTA bodies facilitated through EUnetHTA21

Extrapolation / evidence transfer as a tool to support assessment in smaller populations			
Joint methodological work on the concept of extrapolation / evidence transfer to better understand each other's reasoning for accepting extrapolation	Consult a newly developed regulatory assessment template with HTA bodies		HAS
	Follow-up workshops to exchange of experiences of each other's remits and tasks.		TCV
			HAS

82 **Figure 1: Pediatric Extrapolation Approach**

Pediatric Extrapolation Concept

Similarity of Disease and Response to Treatment Between Reference and Target Pediatric Population

Different disease and/or response to treatment — Same disease and/or response to treatment

Evidence to Support Similarity

No data/large gaps in knowledge — High Quality Data/High Confidence

Types of Data: Clinical Trial Data; nonclinical data; real world data; other sources

Pediatric Extrapolation Plan

Potential Study Designs

Adequate and Well-Controlled Trial(s)	Bridging biomarkers; Other response markers; Bayesian strategies; "modified" frequentist approaches; single-arm PK/PD studies	Exposure matching; Enrollment in or concurrent with adult trials

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14 February 2022
EMA/CHMP/13622/2022
Committee for Medicinal Products for Human Use (CHMP)

ICH harmonisation for better health

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Structured guidance on the use

06 April 2022
EMA/CHMP/ICH/205218/2022
Committee for Medicinal Products for Human Use

ICH guideline E11A on pediatric extrapolation
Step 2b

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf
https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation_.pdf
https://www.ema.europa.eu/en/documents/report/report-implementation-ema-eunethta-21-work-plan-2021-2023_en-0.pdf

Extrapolation - what role for Real World Evidence

			Pharmacology Drug disposition & effect	Disease manifestation & progression	Clinical response to treatment Efficacy & safety
SOURCE POULATION Adults and/or paediatric	Extrapolation concept	Mechanisms	Age/maturation-related differences in - ADME - mode of action - PD effects (E-R) - toxicity	Age/maturation-related differences in - aetiology - pathophysiology - manifestation - progression - indicators	Age/maturation-related - differences, - applicability, - validation of efficacy & safety endpoints
		Quantitative evidence	PB-PK/PD models, Pop-PK/PD models Quantitative systems pharmacology models Covariates: - body size, age, maturation, etc - disease types, severity - comorbidity	Quantitative synthesis of natural disease data Disease progression models Covariates: - age, maturation, etc - disease types, severity - comorbidity	Quantitative synthesis or meta-analysis of treatment data Disease response models Covariates: - age, maturation, etc - disease types, severity - comorbidity
			➢ existing data ➢ progressive input of emerging data		
TION atric subgroups		Inference	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety by paediatric subgroup	Describe/predict differences in natural course of disease progression by paediatric subgroup	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by paediatric subgroup
			➢ refine inferences using emerging data		

Extrapolation plan and mitigation of uncertainties	PK studies or PK/PD studies needed for confirmation of doses in target population Pre-clinical mechanistic studies	Epidemiological data - natural disease course - SOC treatment in target population	- Design of clinical studies - Sample size(s) required in target population to conclude on benefit-risk balance
confirmation of the Extrapolation Concept	Confirm - modelling approaches - identified assumptions - confirm predicted differences in PK and PD Establish appropriate doses in the target population	Confirm predicted differences in disease progression Conclude on disease progression in target population	Confirm predicted differences in clinical response Conclude on positive benefit-risk in target population
	➢ alternatively, adapt extrapolation concept and plan		
Further validation	PK/PD data from - phase III trials - post MA studies	Epidemiological data Other drug developments	Post MA studies Prospective meta-analyses Pharmacoepidemiological data Other drug developments

https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf

Age inclusive research

ICH harmonisation for better health

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06 April 2022
EMA/CHMP/ICH/205218/2022
Committee for Medicinal Products for Human Use

ICH guideline E11A on pediatric extrapolation
Step 2b

979 **5.2 Inclusion of Adolescents in Adult Trials**

980 The enrollment of adolescents into adult clinical trials may hasten a... there be reasons, e.g. lack of equipoise or feasibility making the conduct of an RCT not possible, justifications

981 and The decision to include a pediatric cohort (e.g., an adolescent subgroup 12 to 17 years of age)

982 His in an adult (e.g., > 18 years of age) clinical trial assumes the disease and response to treatment

983 cor are sufficiently similar between the adolescent and adult patients. As such, the objective(s) of

984 ped including adolescents and adults in a single trial should be framed within the context of the

985 bro extrapolation concept. Additional data to inform adolescent dosing may not be necessary as the

986 son adolescent and adult PK are generally similar. In such situations, specific consideration

FDA U.S. FOOD & DRUG ADMINISTRATION

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26 March 2021

Common Commentary - EMA/FDA
Common issues requested for discussion by the respective agency (EMA/PDCO and FDA) concerning paediatric oncology development plans (Paediatric Investigation Plans [PIPs] and initial Pediatric Study Plans [iPSPs])

Paediatric clinical development:

EMA position for PIP applications

Discuss opportunities for inclusion of adolescents in adult studies to accelerate development in this age group, especially in situations where the clinical indication spans the adult and adolescent age group such as in Hodgkin lymphoma, some sarcomas, melanoma, including a discussion on disease similarity allowing to use extrapolation as supporting methodology.

The gold standard remains evidence generation as part of a randomised controlled trial (RCT). However, should

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26 April 2019
EMA/180203/2019
European Medicines Agency
Human Medicines Research and Development Support Division
Paediatric Medicines Office

Prof Gilles Vassal
Chair of Accelerate and President of Innovative Therapies for Children with Cancer in Europe (ITCC)
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Dr Nathalie Gaspar and Chris Copland (Nathalie.GASPAR@gustaveroussy.fr and chriscoplandtyork@gmail.com)
Co-Chairs of the Accelerate Working Group – Fostering Age Inclusive Research (FAIR)

Dear Dr Gaspar, Professor Vassal and Mr Copland

RE: Foster Age-Inclusive Research

The EMA and its Paediatric Committee (PDCO) follow closely and with great interest the Accelerate's FAIR (Foster Age-Inclusive Research) initiative, aiming to facilitate timely access of novel therapies for children with cancer. In this respect the EMA and PDCO took also note of the FDA's Draft Guidance for Industry on 'Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials' (published in June 2018).

The PDCO reviews Paediatric Investigation Plans (PIPs) for medicines for treatment of children with cancer, as mandated by the EU Paediatric Regulation. With the goal of fostering timely studies in the paediatric population, we generally request early initiation of studies in adolescents, either by inclusion of adolescents in adult trials or by conduct of an adolescent trial in parallel to the adult program, whenever this is scientifically justified. Of course, PIPs are evaluated on a case-by-case basis and thus this strategy is not universally applicable.

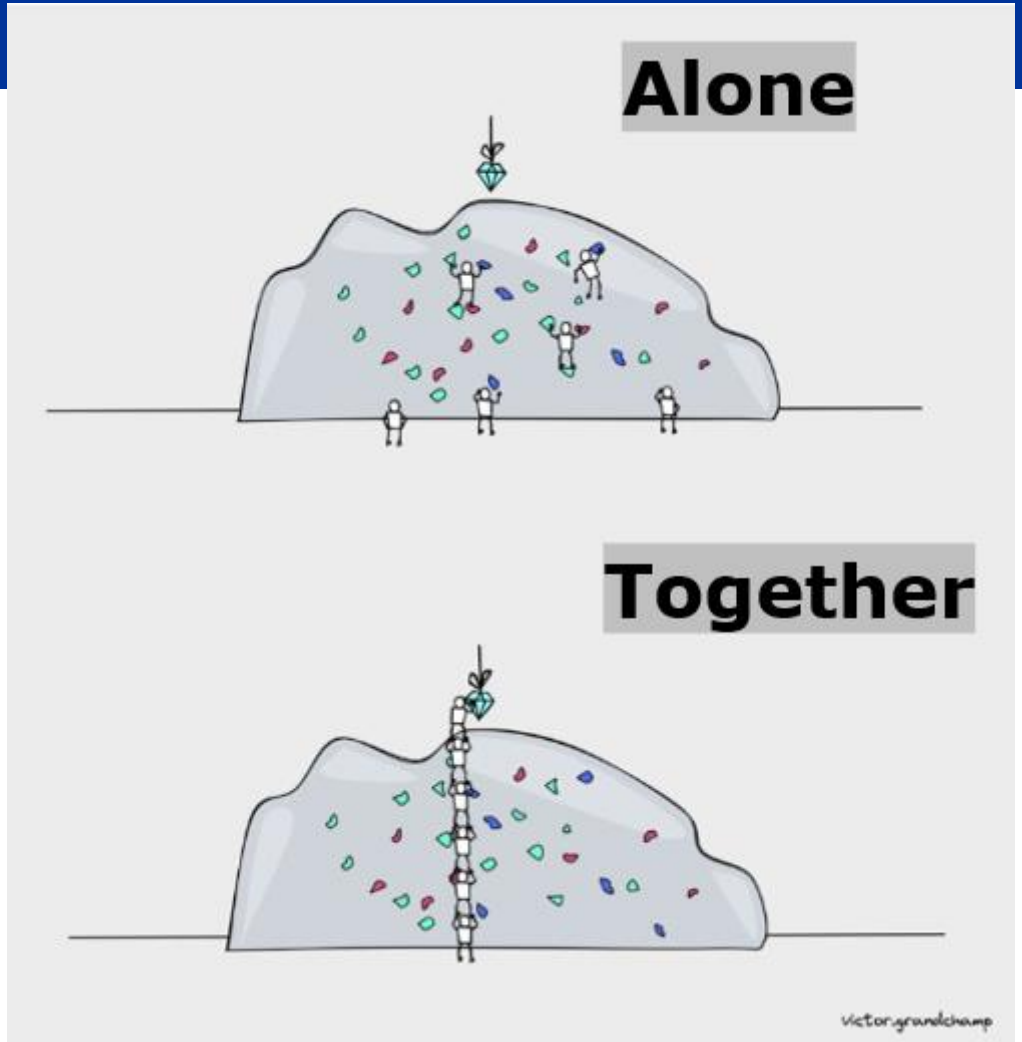
https://www.ema.europa.eu/en/documents/other/common-commentary-ema/fda-common-issues-requested-discussion-respective-agency-ema/pdco-fda-concerning-paediatric-oncology-developn
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf
https://irp.cdn-website.com/c584cf91/files/uploaded/PDCO-letter-to-FAIR-Group-supporting-age-inclusive-research-1.pdf

Conclusion

- Paediatric specificities are driving development(s) of novel methodologies, like use of extrapolation

- Continues need to educate all stakeholders on the adequate use of existing methodology guidance

- Continues need to identify ‘methodology guidance white spots’ to support successful science-based paediatric development efforts and decision making within the eco-system



Acknowledging all colleagues from the PME office and EMAs Paediatric Committee (PDCO)

Thank you!

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