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EMA Extrapolation Framework
Regulatory tools

Workshop on extrapolation of efficacy and safety in medicine development across age groups

Presented in London on 18 May 2016 by Paolo Tomasi MD PhD
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An agency of the European Union

Is extrapolation always a good idea?

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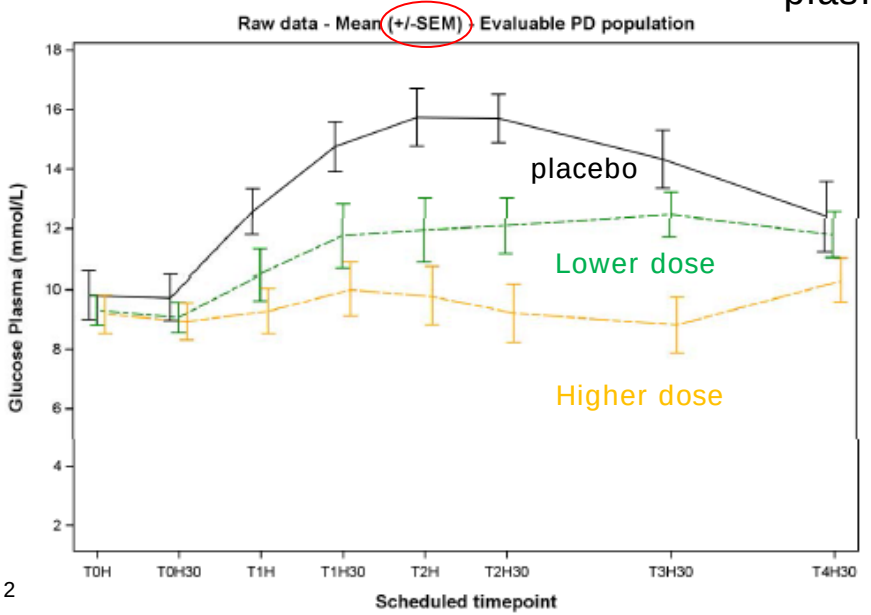
A word of caution: different response to treatments in adults and children

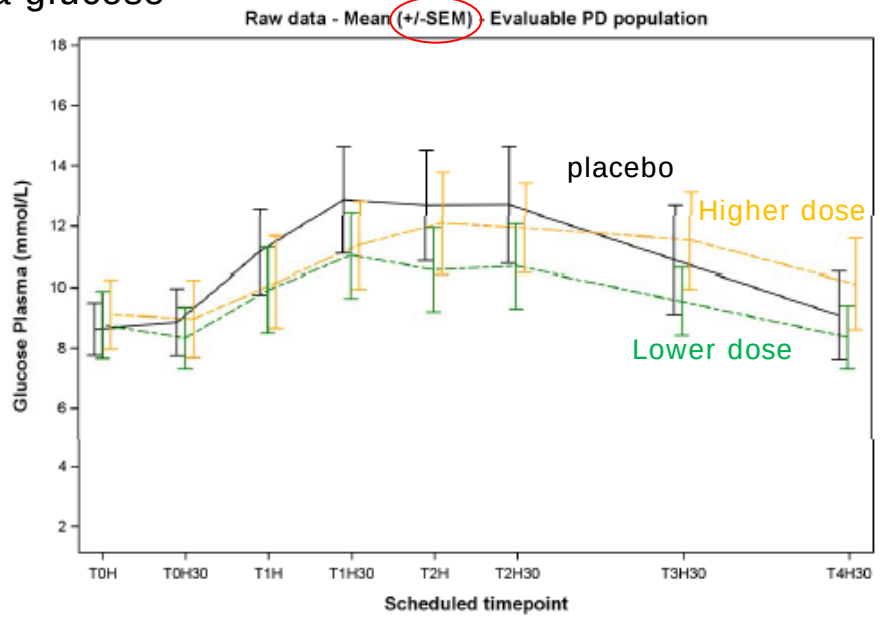
(GLP1 agonist treatment for T2DM)

Adults (N=12)

Postprandial plasma glucose

Adolescents (N=9)

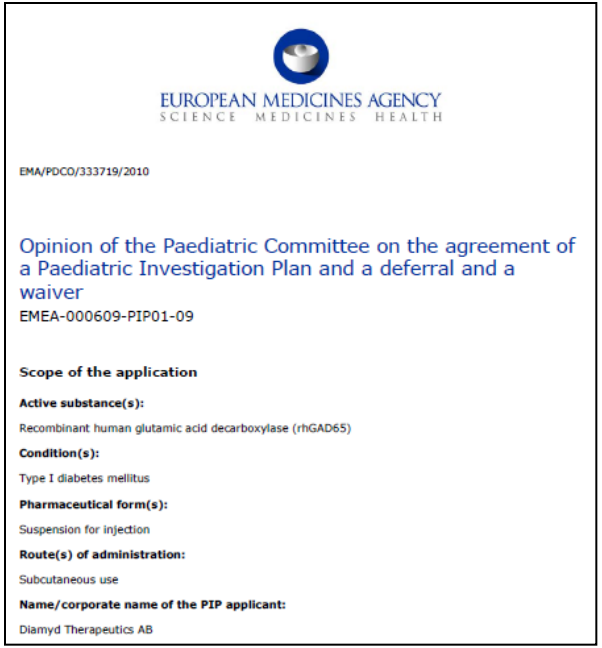




Is paediatric development mandatory in the EU?

Paediatric development is mandatory in the EU for new medicines:

- Unless a product-specific **waiver** or a class waiver (for a class of medicinal products) is granted by EMA
  (waivers apply only for specific medical conditions)
- **Deferrals** can also be granted
  (studies in children can be initiated and/or completed after applying for marketing authorization in other populations or conditions)



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EMA/PDCO/333719/2010

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver
EMEA-000609-PIP01-09

Scope of the application

Active substance(s):

Recombinant human glutamic acid decarboxylase (rhGAD65)

Condition(s):

Type I diabetes mellitus

Pharmaceutical form(s):

Suspension for injection

Route(s) of administration:

Subcutaneous use

Name/corporate name of the PIP applicant:

Diamyd Therapeutics AB

EMA works with own staff (scientific/administrative) + Scientific Committees (nominated by Member States/EC)

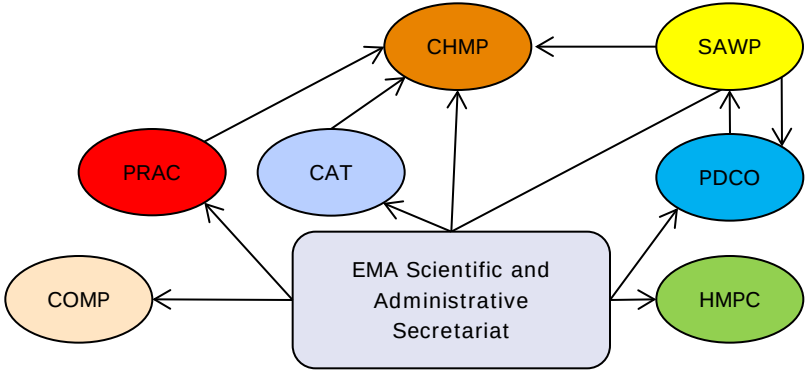
All EMA Scientific Committees are involved with paediatric medicines:

CHMP: authorises medicines for paediatric (and adult) use

PRAC: monitors safety of paediatric (and adult) authorised medicines

CAT: assesses advanced therapies for children (and adults)

COMP: designates medicinal products as orphan drugs, for paediatric (and adult) use



HMPC: discusses herbal medicinal products for paediatric (and adult) use

SAWP: provides scientific advice on medicines being developed for paediatric (and adult) use

PDCO: agrees Paediatric Investigation Plans, Waivers, modifications of plans, checks compliance with plans, advises other Committees / EC on paediatric uses…

What types of extrapolation strategy are possible?

Analysis of extrapolation strategies (efficacy)

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No extrapolation

(full development programme in the target population)

- e.g. paediatric-only conditions, vaccines
- Relatively unusual otherwise, as data in adults are generally available (17% of FDA Written Requests)

"Partial" extrapolation

(reduced study programme in target population depending on magnitude of expected differences and certainty of assumptions)

- Most frequent case (68% in FDA WR)
- Conscious or implicit (unacknowledged)
- Degree of extrapolation may vary substantially

"Complete" ("total") extrapolation

(some supportive data to validate the extrapolation concept)

- e.g. no efficacy study in children. Relatively uncommon but possible (14% in FDA WR)

continuum

Examples of extrapolation continuum

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Definition	Methodology	Notes / examples
Total extrapolation (of efficacy)	No efficacy studies in children	PK, PK/PD or safety study(ies) may still be needed.
Partial extrapolation	Case series, N-of-1 trials	Efficacy may be extrapolated from limited data, not fully powered
	Bayesian designs (simple or adaptive)	Degree of extrapolation depending on the prior distribution(s) and weight
	Adaptive designs (under a frequentist framework)	Efficacy results from adult studies to inform design
	Lower power of efficacy study (provided point estimate and direction of effect are similar in adults)	Non-standard significance level
		Use of fixed, "underpowered" sample size (N=<60 per arm)
		Safety and activity study, not powered for efficacy but with efficacy endpoint(s)
Partial extrapolation (FDA) **No extrapolation (EMA)**	Single efficacy trial	One fully-powered, comparative, randomised, double-blind efficacy and safety study in children of appropriate age group(s)
No extrapolation	Full development in children	Complete development programme required, for example including at least two separate comparative, randomised, double-blind efficacy studies.

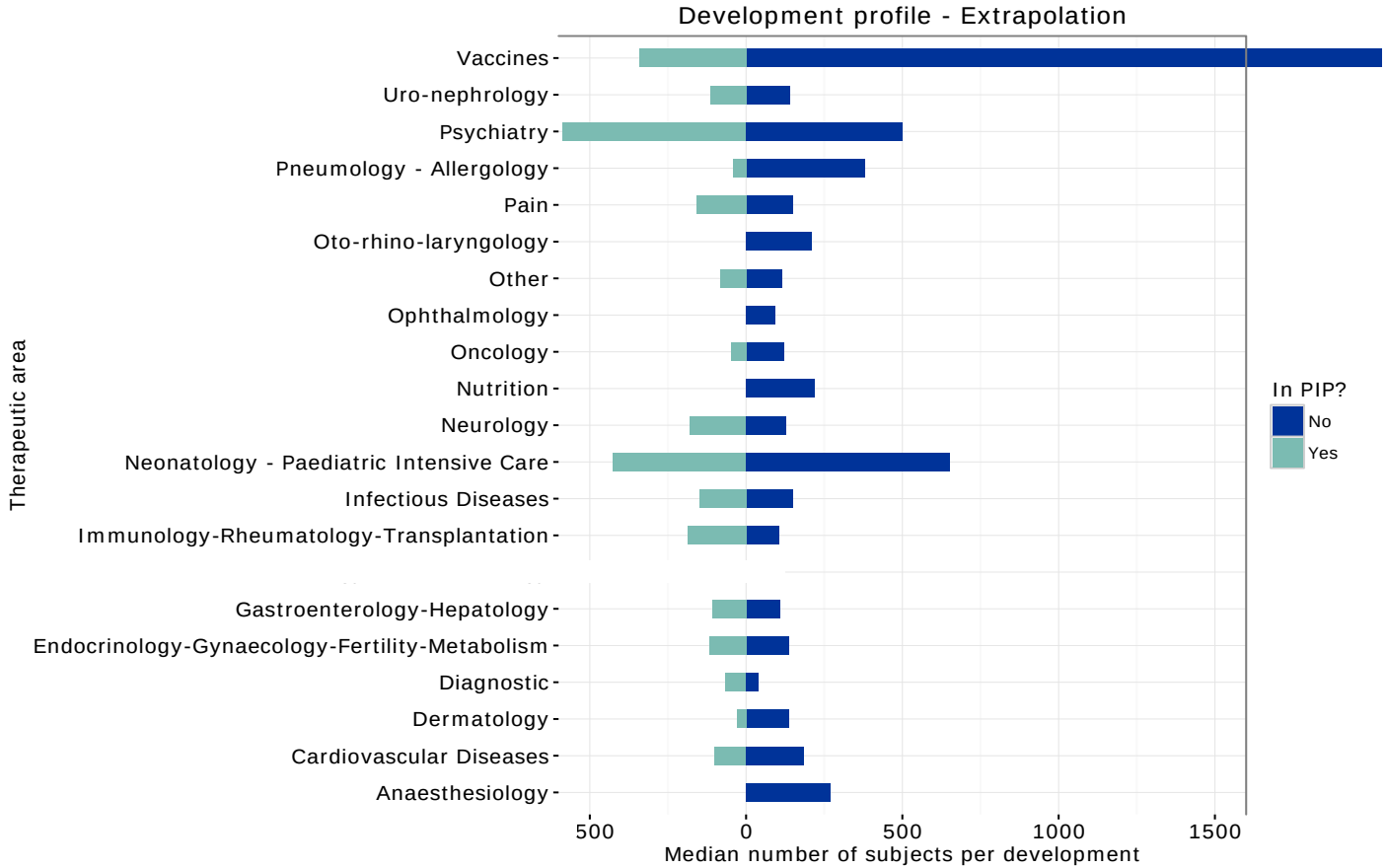
P Tomasi, Journal of Clinical Studies, 5(3):10-16, 2013

Extrapolation continuum: examples accepted in Paediatric Investigation Plans

- PK/PD studies only.
- Dose-ranging or dose-titration studies.
- Non-controlled ‘descriptive‘ efficacy and/or safety study.
- Controlled study, but arbitrary sample size.
- Larger significance level, lower coverage probability of confidence intervals.
- Acceptance of (very) surrogate endpoints for the primary analysis.
- Interpolation (bridging), e.g. between age subgroups.
- Modelling prior information from existing data sets (Bayesian models, meta-analytic predictive).

Is sample size affected by the use of extrapolation?

Impact of extrapolation on sample size



- Median total number of children to be recruited is generally lower when extrapolation is part of the development plan
- However impact varies by therapeutic area and may not always lead to reduced sample sizes
- This is in line with the understanding that measures to extrapolate efficacy are relevant to strengthen the development and the interpretation of paediatric data; only as a consequence, the sample size may be reduced in some cases.

Is extrapolation accepted in EU Paediatric Investigation Plans?

Extrapolation in PIPs

- 52 PIPs agreed with explicit extrapolation measures/studies (2007-2015)
- Extrapolation is generally limited to efficacy
- EMA Modelling and Simulation Working Group:
  - ✓ Provides specialist scientific support on modelling and simulation to the SAWP, PDCO and CHMP
  - ✓ 2015: 47 out of 90 referral procedures originated from PDCO

Treatment of acute venous thromboembolism

A. Biological/pharmacological rationale

- Different underlying disease 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

Agreed PIP 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

Extrapolation in initial PIP decisions – other examples

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Condition	Age group	Notes
Treatment of HIV1 infection	2-18y	Fixed-dose combination, extrapolation from studies with single substance products
Neutropenia (chemotherapy-induced)	0-18y	Only PK/PD study, active controlled, is performed
Pulmonary hypertension	12-18y	Extrapolation from results in younger age groups
Prevention of *Borrelia* infection	1m-18y	Safety study only
Prevention of invasive fungal infections	1m-18y	PK and safety only. Based on M+S
Perinatal asphyxia	Preterm	Efficacy is extrapolated in preterm neonates from data in neonates and infants
Prevention of smallpox	0-18y	Extrapolation “forced”, as trial unfeasible

Extrapolation in initial PIP decisions – other examples

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Condition	Age group	Notes
Gastroesophageal reflux disease / HP eradication	Neonates	From studies in older paediatric age-groups
Intra-abdominal infection	1m-12y	From studies in older paediatric age-group
Haemolytic-uremic syndrome from Shiga-toxin *E. coli*	0-2y	From studies in older paediatric age-groups
Induction of cardioplegia during surgery	6-18y	From studies in younger paediatric age-groups
Opioid-induced constipation	12-18y	From studies in younger paediatric age-groups
ADHD	2-6y	From studies in older paediatric age-groups
High-grade glioma	1m-18y	Safety only, with external controls

Instances where significant amounts of extrapolation are accepted more often

- Anti-infective products, oncology (20% of PIPs)
- Fixed-dose combination products
  (extrapolation from individual active substances)
- Main paediatric interest is in younger age groups
  (efficacy can be extrapolated from younger children and adults to older children/adolescents)
- “Bioterrorism” products
  (e.g. anthrax or smallpox vaccines and treatments)

Instances where extrapolation is less likely to be acceptable

- Diseases that may appear similar in paediatric patients and adults, but underlying physiology suggests a difference - many failed trials
- Neurologic/psychiatric conditions:
  - SSRIs, antidepressants in general
- Pneumology, allergology
- Vaccines

Where to go (first) to discuss paediatric extrapolation?

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preferred

Early interactions:
- **PRIME**
- **Early paediatric interaction**
- *Business pipeline meeting*

Orphan designation

SME Office

Formal PIP appl. @PDCO

Innovation Task Force briefing meeting

Scientific Advice

Does not matter – come to EMA early, come often

Scientific Advice vs.PIP/waiver procedures

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	PIP / waiver procedure	Scientific Advice (SA)
Legal status	Mandatory (for new products)	Optional (for all products)
Outcome	EMA Decision – Binding for applicant (compliance check before MAA validation)	CHMP letter – Not binding for applicant
Fees	None	None if only paediatric development is discussed. Advice for use in adults has fees
Scope	Global development, including quality, non-clinical and clinical aspects, and timelines	Answers specific questions from companies
Responsible group @ EMA	Paediatric Committee (PDCO)	Scientific Advice Working Party (SAWP) / Comm. for Human Medicinal Prod. (CHMP)
Ideal timeline of first contact	As early as possible – at the completion of phase I studies in adults – always before starting studies in children	As early as possible – at any time
Which one first?	In many cases, companies may wish to agree a PIP first, and specify further details with SA later. Company may choose freely in any case	For specific questions affecting development in both adults and children (quality, joint trials) SA first is advisable

Agreeing a paediatric development plan

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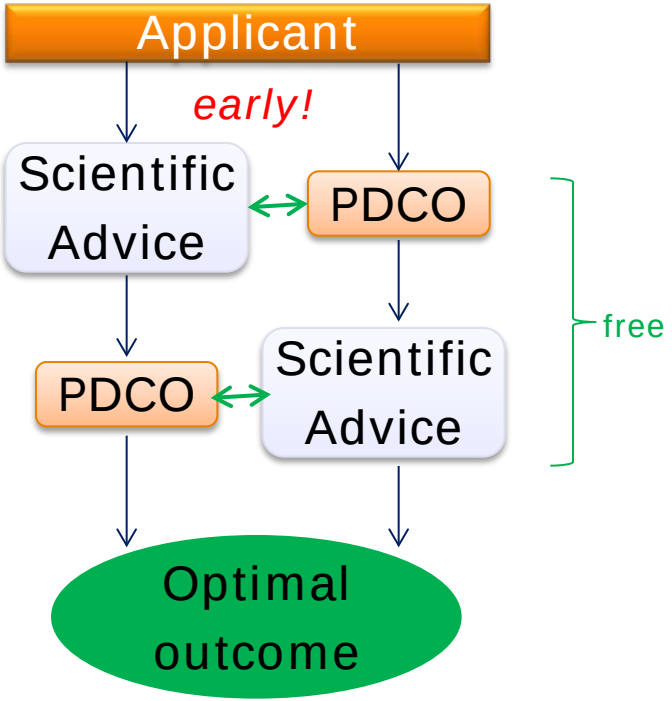
- **The Paediatric Investigation Plan must be discussed and agreed early, long before Marketing Authorization is requested**
- **and before trials are started in children!**
- **Agreeing a PIP takes on average 8-12 months from start to finish**



Come to EMA early, come often!

How do I describe my proposed extrapolation study?

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- Adaptive pathways
- Scientific guidelines
- Innovation Task Force
- Supporting SMEs
- Paediatric medicine
  - Paediatric Regulation
  - Workshops
  - Research and development
  - Paediatric investigation plans
    - PIPs: Questions and answers
    - Standard PIPs
    - Paediatric formulations
    - Class waivers
    - Templates, forms and submission dates
  - Mailing list
  - Rewards and incentives for paediatric medicines
  - Funding for paediatric

Templates and forms

Document(s)	Language	Status	First published	Last updated
Early paediatric interaction meeting template	(English only)		16/06/2015	
Notification of discontinuation of a paediatric development which is covered by an agreed paediatric-investigation-plan decision	(English only)		02/04/2013	01/04
Template for scientific document (part B-E) for application for paediatric investigation plan including deferral and waiver	(English only)		15/02/2013	21/01
Template for notification of change of the paediatric-investigation-plan / waiver applicant / addressee	(English only)		06/10/2010	
Template for letter of intent to submit an application	(English only)		04/01/2010	21/01
Electronic form for paediatric -investigation-plan application and request for waiver - (PED1) certified	(English only)		28/05/2009	06/10
Key elements form: Applicant's proposal for a paediatric-investigation-plan opinion	(English only)		04/01/2010	26/03

Key elements of a modelling and simulation study, proposed to be included in the PIP opinion

Remove this study ▲
Insert study below ▼

1463504630452

Study Identifier(s)

Model description and objective(s)

Extrapolation studies (currently 1 study)

Key elements of an extrapolation study, proposed to be included in the PIP opinion

Remove this study ▲
Insert study below ▼

1463504504977

Study identifier(s)

Study description (Type of study, study design)

Study objectives

Methodology

Study population and subset definition (incl. stratification)

Number of study participants by paediatric subset (e.g., age, sex, stratum)

Date of initiation — *Additional requirements:*

Deferral for initiation requested? ○ Yes ○ No

Date of completion — *Additional requirements:*

Deferral for completion requested?

○ Yes ○ No

Conclusions

1) Extrapolation of efficacy is a useful tool in paediatric drug development, that can be used when appropriate, and should be discussed
2) EMA has accepted extrapolation approaches, when appropriate and properly justified
3) Pharmaceutical companies/sponsors should **come early to EMA** to discuss extrapolation approaches

Thank you for your attention

London – Canary Wharf

Further information

Contact:
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Send a question via our website www.ema.europa.eu/contact

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Backup slides

Qualification of biomarkers

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1. To be requested to Scientific Advice Working Party @ EMA
2. 2 types of procedure:
    1. CHMP Qualification **Advice Letter** on protocols and methods that are intended to develop a novel method with the aim of moving towards qualification (prospective).
    2. CHMP Qualification **Opinion** on the acceptability of a specific use of a method, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to non-clinical or to clinical studies, such as the use of a novel biomarker. (post-hoc)
3. Who can apply? Consortia, Networks, Public / Private partnerships, Learned societies, Pharmaceutical industry
4. Procedure is free for Paediatric development

Both can be made public if applicant consents (100% of Opinions so far)

Scope for Qualification Procedure:

Preclinical development

- pharmacological screening
- mechanism of action
- predict activity/safety

Clinical development

- verify mechanism
- dose-response
- proof of concept
- enrich population
- surrogate endpoint

Drug utilisation

- optimise target population
- guide treatment regimen

EU Paediatric Regulation: obligations versus incentives

Type of MP	Obligation	Incentive	Comments
New# medicinal product	Paediatric Investigation Plan or Waiver	6 months extension of SPC (patent) *	Necessary for **validation** of application
On-patent and authorized medicine	Paediatric Investigation Plan or Waiver	6 months extension of SPC (patent)*	When new indication or new route or new pharmaceutical form: necessary for **validation**
Orphan-designated medicine	Paediatric Investigation Plan or Waiver	2 additional years of market exclusivity*	In addition to 10 years
Off-patent medicine	None (voluntary PIP possible for PUMA)	10 years of data protection	Research funds Paed. Use MA (PUMA)

**if compliance with PIP, information, approval EU-wide*

#*according to GMA concept, and not necessarily a new active substance*

Differences EU (Paed. Regulation) / USA (BPCA-PREA-FDASIA)

	US BPCA	US PREA	EU
Development	Optional	Mandatory	Mandatory *(optional for off-patent)*
Instrument	Written Request	Paediatric Study Plan	Paediatric Investigation Plan
Waiver	N/A	3 grounds	3 grounds
Timing	End of phase 2	End of phase 2	> End of phase 1
Reward	6-month exclusivity	-	Main: 6-month SPC extension (patent)
New drugs	Yes, with exclusivity	Yes	Yes
Biologicals (most)	Yes	All	All
Orphan products	Included	Excluded	Included
Decision	FDA	FDA	EMA (not EC) Opinion: Paed. Committee
Scope of paed. development	not limited to adult indication	= adult indication	Derived from adult indication
Scientific advice	Normally in global fee	Normally in global fee	Free for paediatrics