Pediatric drug development - do we need a PIP so early in development?

American versus European approach

Angelika Joos
Executive Director, Global Regulatory Policy
Merck Sharp & Dohme (Europe) Inc., Brussels

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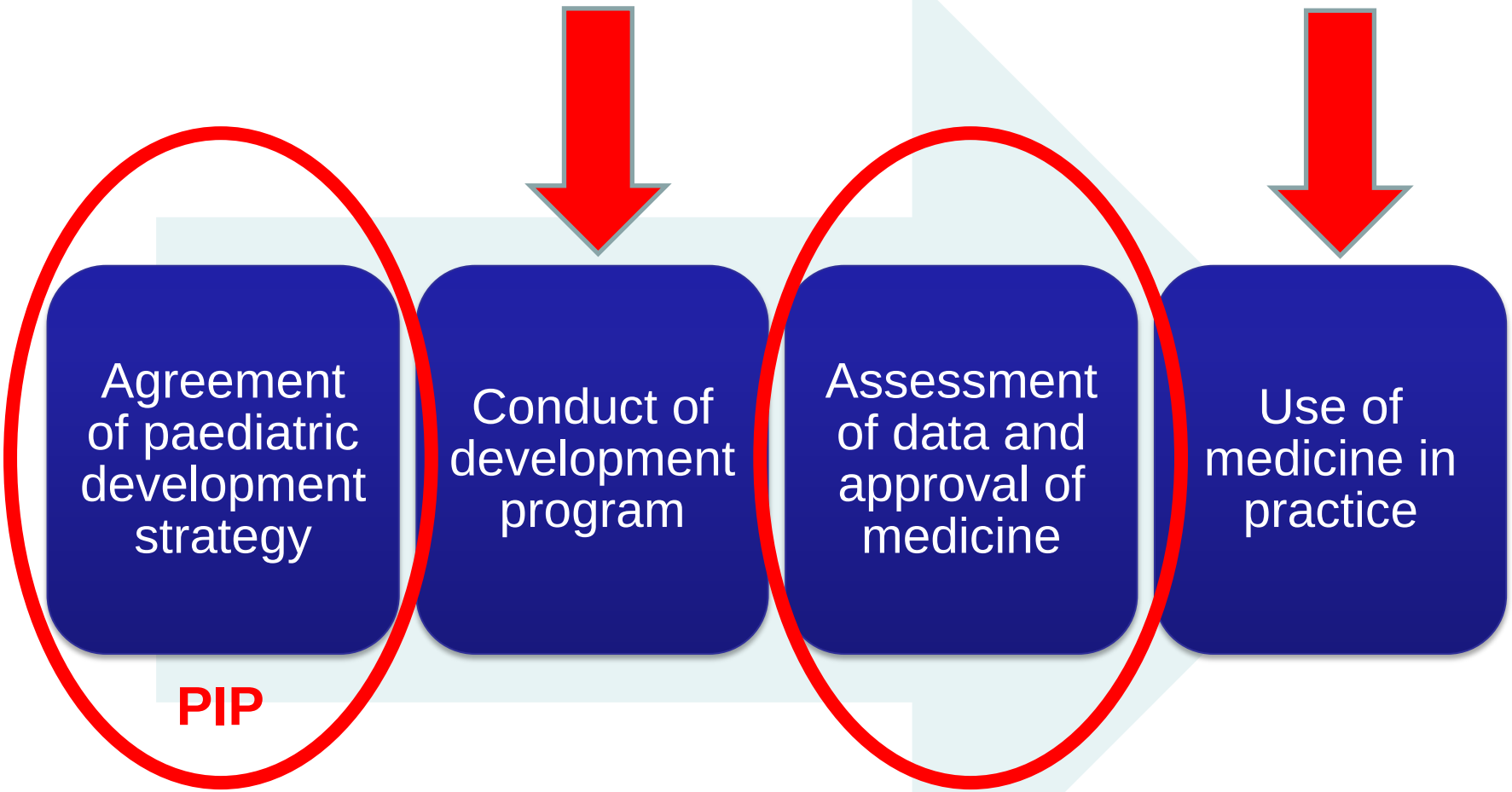
What is the dilemma?



EU Environment: Pediatric Regulation (2007)

Pediatric Investigational Plan (PIP): The basis of development. It is binding and must be agreed to by PDCO and the sponsor. The PIP must be submitted no later than upon the completion of adult PK studies, or sometimes, in practice, proof of concept. PIP must be approved prior to submission of the initial adult marketing authorization application.

Pediatric Committee (PDCO): PDCO assesses the content of the Pediatric Investigational Plan (PIP), including requests for waivers or deferrals. Consists of CHMP & member states representatives plus patient and healthcare professional representatives.

Incentives: upon the inclusion of data in the product information (positive or negative), the drug is eligible for 6 months of patent extension.

Orphan-designated drugs must also have PIPs. Upon approval, orphan drugs qualify for 2 additional years of exclusivity.

Waivers may be granted if:

1. the product is ineffective or unsafe in children or
2. the disease or condition occurs only in adults or
3. the treatment does not represent a significant therapeutic benefit.

- Feasibility may also be taken into account in Section D of the PIP in which operational challenges may be discussed.

European Network of Pediatric Research at the EMA (Enpr-EMA): research network of pediatrics clinical research specialists designed to foster high-quality and ethical research.

Sources: EMA. www.emea.europa.eu, Zisowsky J, Krause A, and Dingemanse J (2010) Drug development for pediatric populations: Regulatory aspects. Pharmaceutics 2:364-388.,

US Regulatory Environment:
Pediatrics Provisions Made Permanent by FDASIA (July, 2012)

Pediatric Research Equity Act (PREA): requires sponsors to provide FDA with pediatric assessment plans prior to the time of the NDA (with deferrals and waivers) and grants FDA the authority to mandate trials in pediatric populations related to the conditions of approval for the adult indication.

Best Pharmaceuticals for Children Act (BPCA): grants six months of additional exclusivity to products containing the active moiety for which sponsors conduct requested pediatric trials.

PREA does not apply to drugs for which orphan designation has been granted.

Process:

- Pediatric Review Committee (PeRC) reviews all Written Requests (WR), deferrals, waivers, and serves as a consultant to the review divisions who review submitted studies in response to requests.
- Pediatric Plan must be submitted shortly after the end of phase 2 meeting. This outlines all studies the applicant plans to conduct (including formulation development, PK/PD, safety, efficacy) plus any requests for deferrals or waivers. May be amended at any time.
- To qualify for the BPCA incentive: Sponsor responds completely to the WR with completed study reports and the FDA determines that the study reports are fully responsive to the WR.

Pediatric Rare Diseases: Per FDA Safety and Innovation Act (FDASIA), FDA is considering additional plans to encourage and accelerate new treatments for rare diseases.

Sources: FDA Guidances for Industry, www.fda.gov, Zisowsky J, Krause A, and Dingemanse J (2010) Drug development for pediatric populations: Regulatory aspects. Pharmaceutics 2:364-388.

EU-US Pediatric Legislative Differences

	US BPCA	US PREA	EU
Development	Optional	Mandatory	Mandatory (off-patent optional through PUMA)
Instrument	Written Request	Adult submission	PIP
Waiver	--	3 grounds for full and 4 grounds for partial	3 grounds for full or partial
Timing 	End of Phase 2 thru post-marketing	~~With NDA adult submission~~ ***<60d post EOP2 Mtg***	End of human pk studies in adults
Reward	6 months patent ***(WR Must Be Issued for Eligibility)***	***PREA Studies Can Qualify for Exclusivity***	6 months patent (Possible 10 yr data exclusivity for PUMA)
Drugs (Section 505)	Yes	Yes	Yes
Biologicals	Yes	Yes	Yes
Orphan	Included	Excluded	Included
Decision	FDA	FDA ***(Divisions must seek PeRC review on PSP)***	EMA- PDCO

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Thanks to Imo Ibia, Adapted from Ron Portman, DIA 2010

Timing of PIP submission

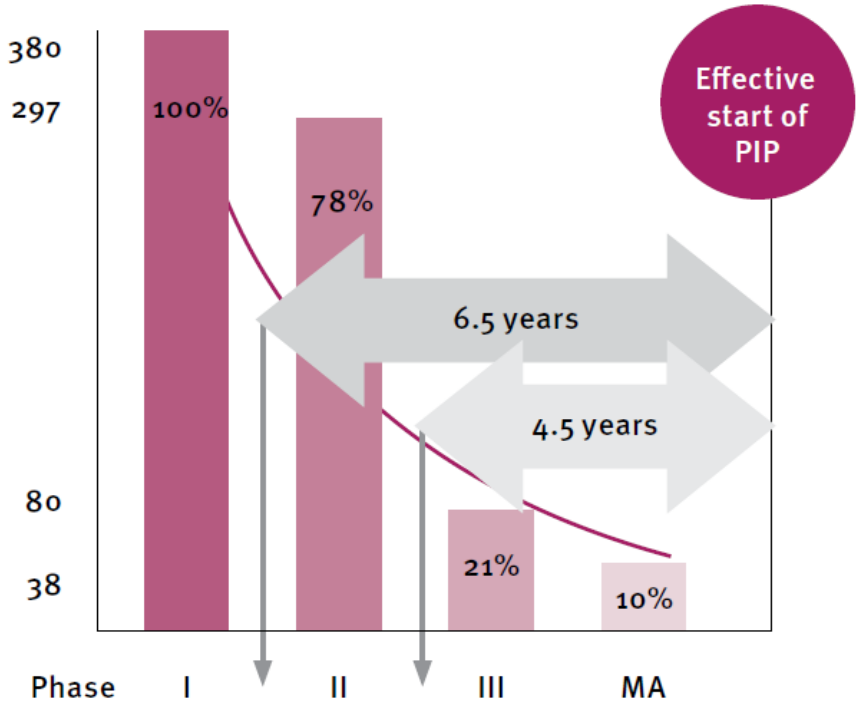
Too early submission based on limited data creates unnecessary follow up activity

- PIPs require between 4-10 amendments
  - 20% are major changes that alter their conceptual construct

The scientific context can significantly change until the paediatric studies actually start

- Average time between approval of initial PIP and first paediatric study: 7 years
- Average time between first adult approval and completion of PIP: 6,5 years
- > 80% attrition rate of adult drug candidates entering Phase I
  - There is no mechanism to withdraw a PIP

Figure 1: Timespan from PIP submission to adult MAA and attrition rate of 380 candidate drugs entering Phase I.

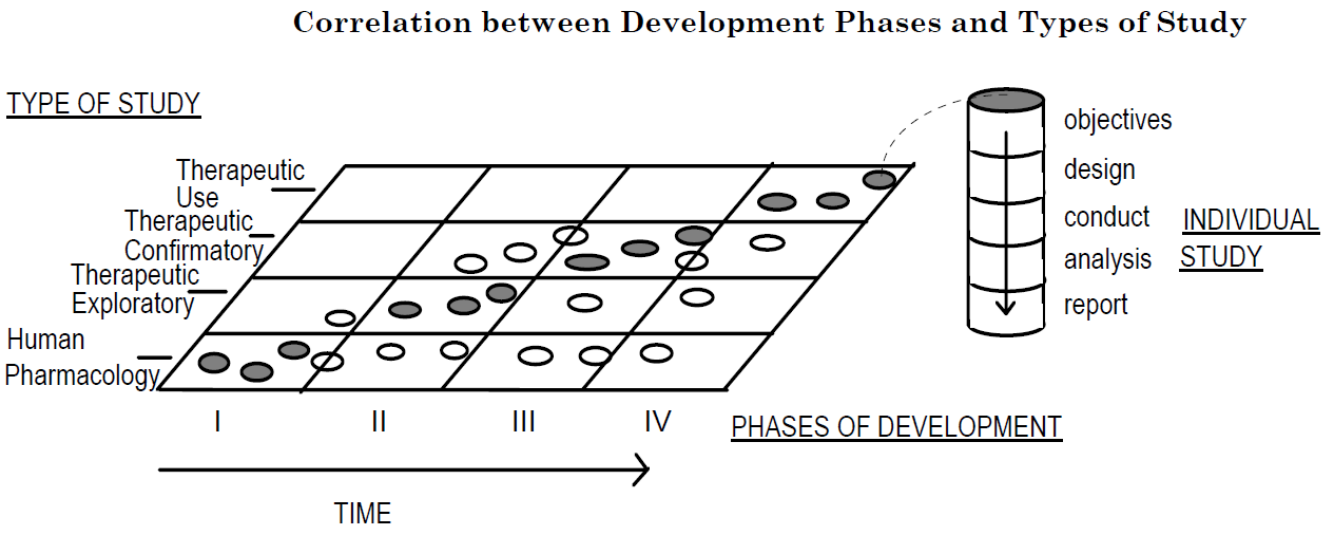


Source: Brasseur, Understanding the Paediatric Regulation: Who got the wrong end of the stick?, Regulatory Rapporteur, March 2014

Timing of PIP submission

"Completion of human pharmacokinetics studies in adults" **provides an inadequate criterion** for setting a deadline for the submission of a PIP

- For example, although human pk studies are typically conducted during Phase I, many such studies are conducted at each of the other three stages



Source: ICH E8, 1997

Timing of PIP submission

Practical considerations to smoothly integrate paediatric development into companies' drug development process should be taken into account for the timing

- Development focus and data generation mainly driven by specific adult indication
- Key milestone decision point to move into phase III trials (≈50% of R&D cost)
  - Late stage development programs have naturally more allocated resources
- Fixed amount of R&D funds per FY to cover **all** company development activity

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Timing of PIP submission

Coordination of development program discussion with EU and US regulators to achieve compatible paediatric plans is **required from an ethical perspective** to avoid unnecessary trials in children.

- FDA legal requirement: submission of Pediatric Study plan 60 days after the end of Phase II meeting
- Encourage simultaneous discussion with both agencies
- EMA/FDA Paediatric cluster discussions
- Full support for ICH E11 Q&A discussion

What is the dilemma?

Regulatory expectation to discuss detailed paediatric investigational plan very early during R&D process

Opportunities for paediatric data collection alongside adult development

Start paediatric development to get medicines for children earlier

Insufficient data to design informed development strategy or start clinical trials

Wasted regulatory resources due to high attrition rate

Incompatible with current global medicine development process

Which elements should be agreed?

According to the Regulation, a PIP is a development **concept** (German translation: Pruefkonzept) that should be agreed **early** with Regulators

Important questions to seek agreement on*:

- Is the candidate drug of paediatric interest? (If not, agree to a waiver)
- In which indication?
- For which age group (is there a need for specific formulations, additional juvenile studies)?
- What type of clinical program (eg partial extrapolation, pk only, full extrapolation)?
- Limit the PIP to one indication!

*Source: Brasseur, Understanding the Paediatric Regulation: Who got the wrong end of the stick?, Regulatory Rapporteur, March 2014

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Future: EMA early dialogue pilot

- Timing: very early and in advance of a PIP application
- Objective: discuss the potential paediatric needs for the medicine and the scope of its development for use in the paediatric population, taking into account the properties of the future medicinal product and its overall development.
- Format: video- or teleconference with EMA and PDCO

When to start paediatric trials?

- Diseases affecting predominantly or exclusively paediatric populations:
  - Initiate studies in the initial phases of the product development
- Medicinal products intended to treat serious or life-threatening conditions & currently no or limited treatment options
  - Begin clinical development early following assessment of initial safety data and reasonable evidence of potential benefit
- Medicinal products for other diseases and conditions:
  - Begin in Ph 3, when the therapeutic effect and a potential dose-range have been established in adults

➢ General Practice for **new molecule classes and novel MoA**:

- Obtain further safety data from adult use after initial registration before conducting paediatric studies

Source: ICH E11

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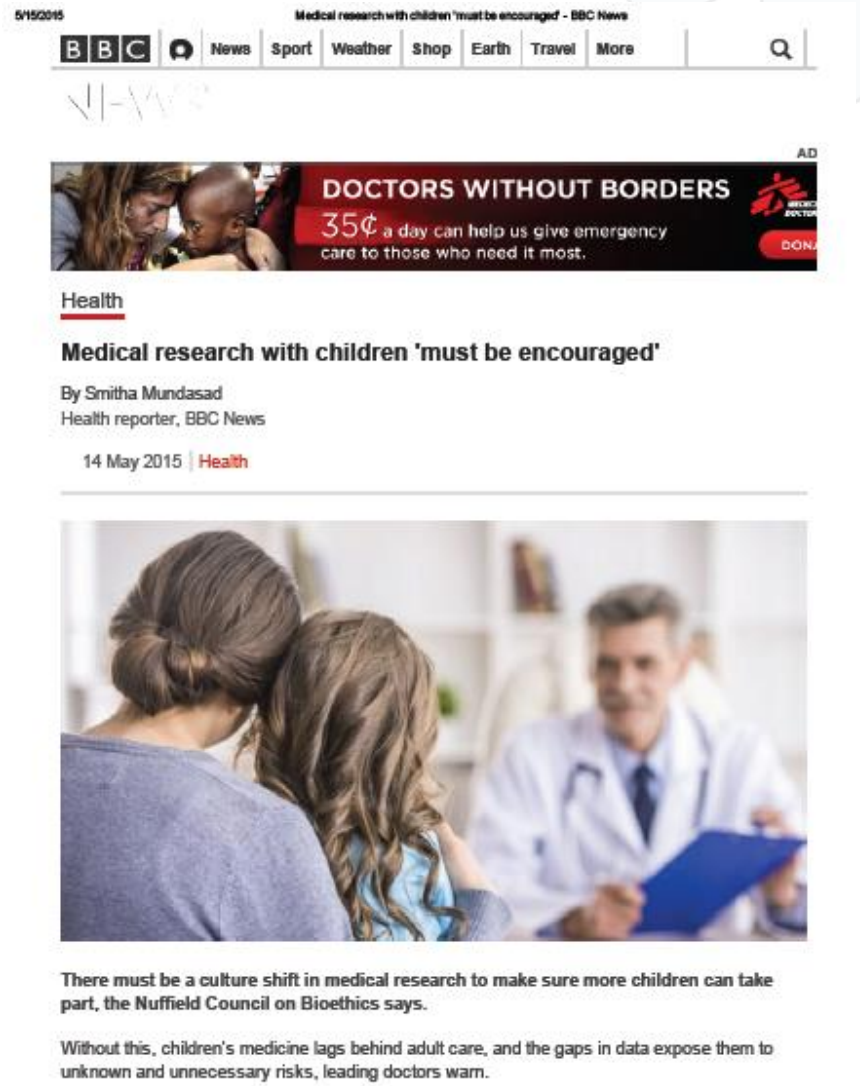
What is the dilemma?

Ethical assumption that children should always be considered a vulnerable group that needs to be shielded from research

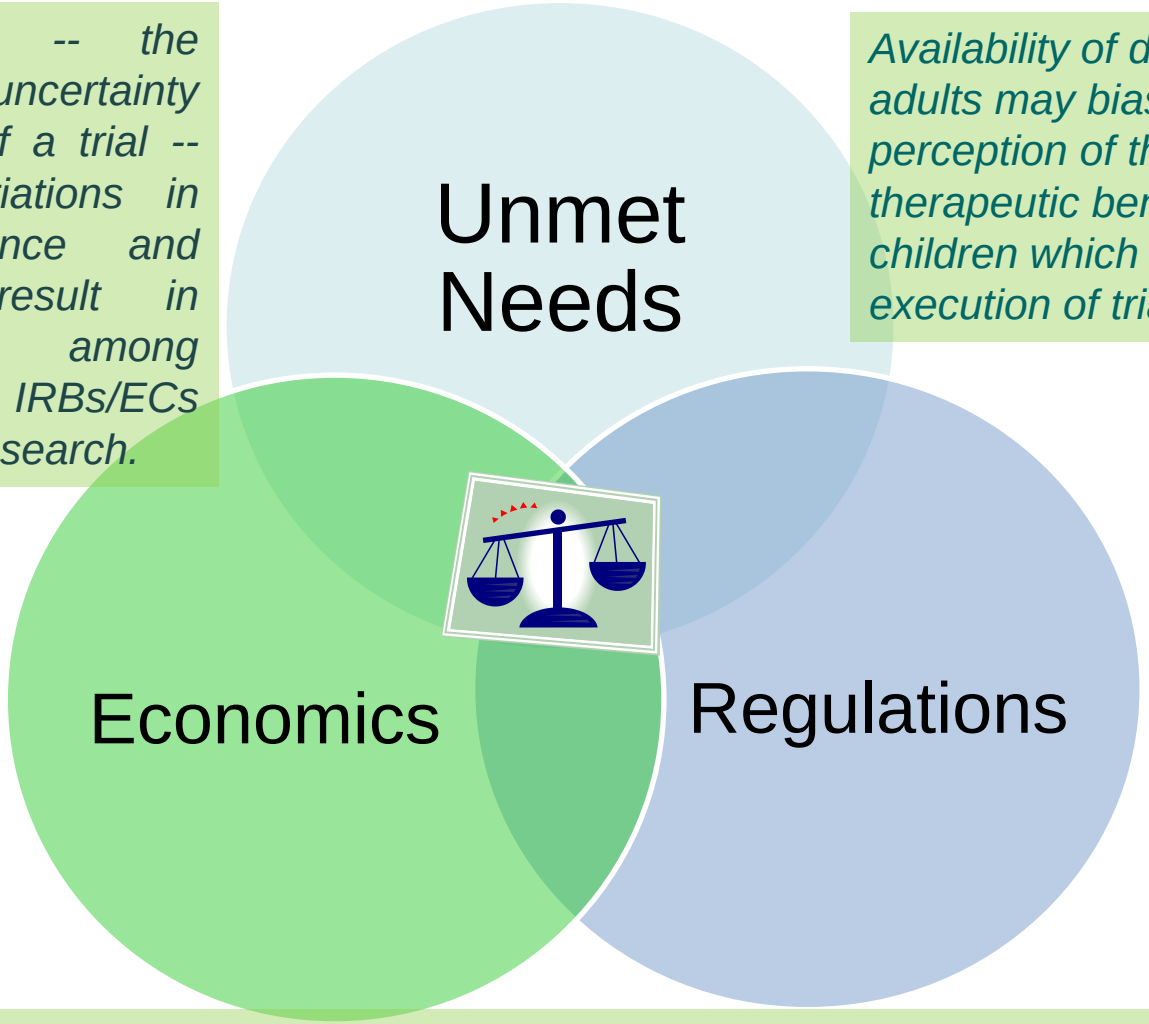


Tipping Point

Clinical Equipoise, Therapeutic Bias, and Research Ethics

Clinical equipoise -- the required clinical uncertainty driving each arm of a trial -- must exist. Variations in quality of evidence and practices may result in disagreements among investigators and IRBs/ECs which could delay research.

Availability of drugs for adults may bias the perception of their therapeutic benefit in children which may delay execution of trials.



IRBs/ECs protect children based on interpretations of equipoise, potential risks, and harms. EMA: Advocating increasing collaboration between ECs and PDCO.[1]

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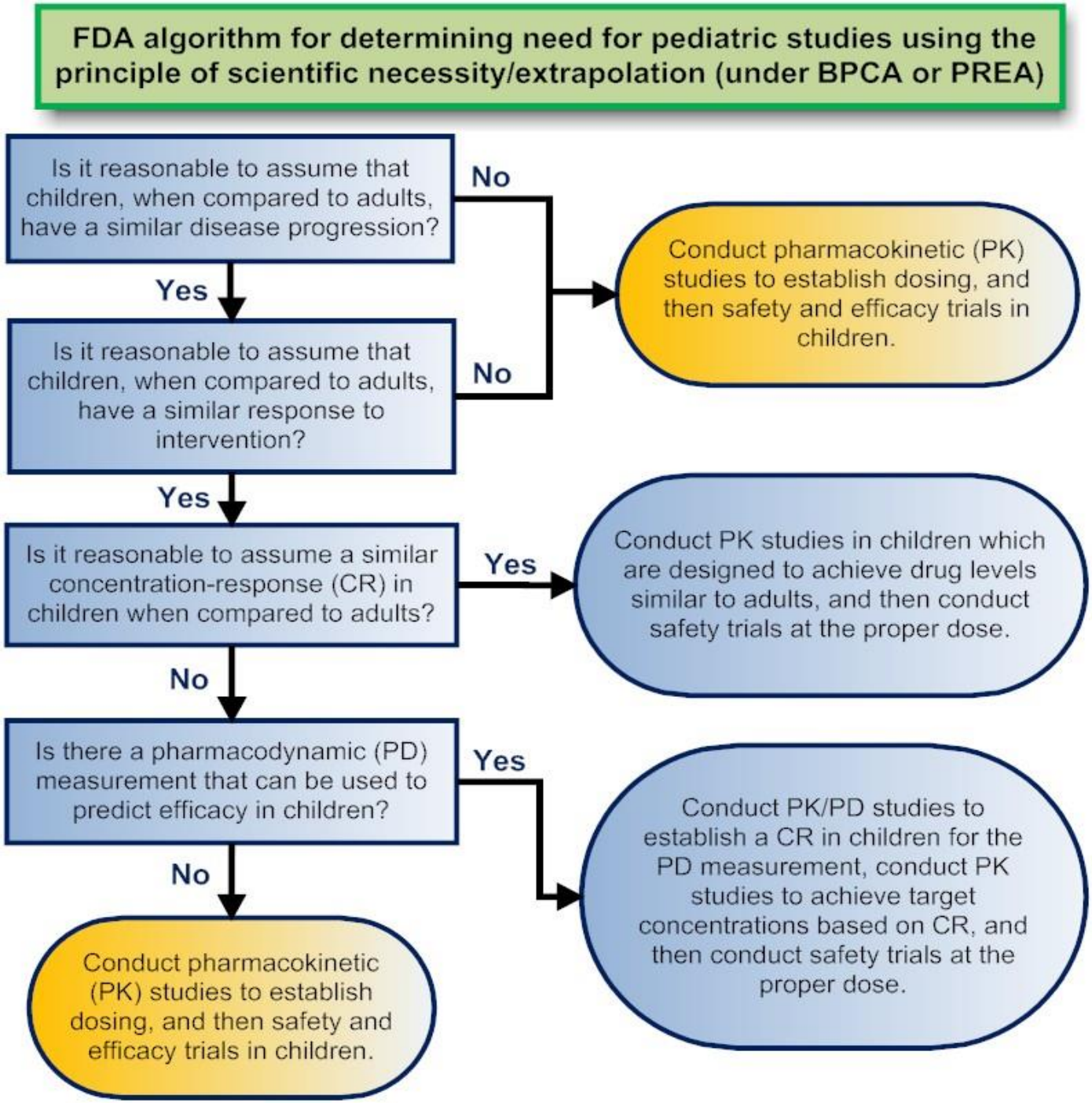
Sources: Bates KE et al (2012). Pediatric cardiovascular safety: Challenges in drug and device development and clinical application . EMA Guidance October 18, 2012: Ethical considerations for paediatric trials. Report on an international meetings at the EMA 30 Nov – 1 Dec 2011


FDA algorithm for determining need for pediatric studies using the principle of scientific necessity/extrapolation (under BPCA or PREA)
Is it reasonable to assume that children, when compared to adults, have a similar disease progression?
No
Yes
Is it reasonable to assume that children, when compared to adults, have a similar response to intervention?
No
Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.
Yes
Is it reasonable to assume a similar concentration-response (CR) in children when compared to adults?
Yes
Conduct PK studies in children which are designed to achieve drug levels similar to adults, and then conduct safety trials at the proper dose.
No
Is there a pharmacodynamic (PD) measurement that can be used to predict efficacy in children?
Yes
Conduct PK/PD studies to establish a CR in children for the PD measurement, conduct PK studies to achieve target concentrations based on CR, and then conduct safety trials at the proper dose.
No
Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.

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Modelling & Simulation and Extrapolation

- Use of M & S in pediatrics is encouraged and increasing, *with potential effect on adult development !*
  - Role in design & analysis of drug studies in pediatrics
  - Methodologies to be continually evaluated, refined, tailored
  - Joint responsibility and effort of industry, health authorities, and academia
- More research and collaboration is required to support the science

Should there be Innovative Medicine Initiative (IMI) projects to develop the regulatory science together?

1 Ibrahim Ince, Drug Discovery Today Volume 14, Numbers 5/6 March 2009
2 http://www.ncbi.nlm.nih.gov/pubmed/24440429

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Opportunities for the Future

- The PIP discussion could **focus on the strategy** to investigate the essential key elements and integrate the detailed scientific debate into the overall regulatory development framework at the time when action happens

- The agreement on the PIP strategy could be postponed, **without any delay of the start of paediatric studies** compared with the present scenario
  - Based on more comprehensive data sets and focused on compounds that will most likely reach the market

Opportunities for the Future

Additional **multi-stakeholder efforts** are required to improve **science and research infrastructure** to enhance the medical situation