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Changes in the Drug Development Landscape: Pediatric Development Is No Longer An Option

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Today's Agenda



- Background on Pediatric Clinical Research
- Pediatric Regulatory Landscape
- Specificities of Pediatric Trials
- Key Considerations for Successful Pediatric Trials
- Conclusion



Background on Pediatric Clinical Research

Current Environment for Pediatrics



- Lack of medicines specifically approved to treat pediatric patients and pediatric diseases
 - High “off-label” use of drugs in children
 - ~50% across all therapeutic areas; >90% in neonates in Intensive Care Unit
 - Little or no formal evaluation of safety and efficacy
 - Imprecise and variable dosing. High use of “Extemporaneous Formulations”
- Challenges in pediatric research
 - Limited market: Fewer drugs prescribed for shorter period
 - High development costs
 - Limited number eligible trial subjects
 - Not a harmonized population (different age groups)
 - Complex Informed Consent and Assent process
 - Fear or inconvenience of parents to let their child participate
 - Lack of appropriate rules for conducting pediatric trials, including with regards to ethical considerations
- Need for appropriate investigation of drugs in children has been recognized
 - Introduction of Pediatric Regulations



Pediatric Regulatory Landscape

Pediatric Regulations – Primary Objectives



- Improve the health of children
 - Increase quality and ethical aspects of pediatric research
 - Increase availability of authorized medicines for children
 - Increase information on medicines for children
- Achieve the above
 - Without unnecessary studies in children
 - Without delaying authorizations for adults

A Shift in Mindset

**“Protecting Children
From Research”**

to

**“Protecting Children
Through Research”**

Regulatory Landscape for Pediatrics



■ United States - FDA

- Pediatric Use, Subsection of the USPI (1979)
- Pediatric use labeling rule (1994), FDAMA (1997)
- **Best Pharmaceuticals for Children Act (BPCA)(2002&2007)**
- **Pediatric Research Equity Act (PREA) (2003)**
- FDASIA (2012) & **FDARA incl. RACE Act (2017)**

■ Europe - EMA

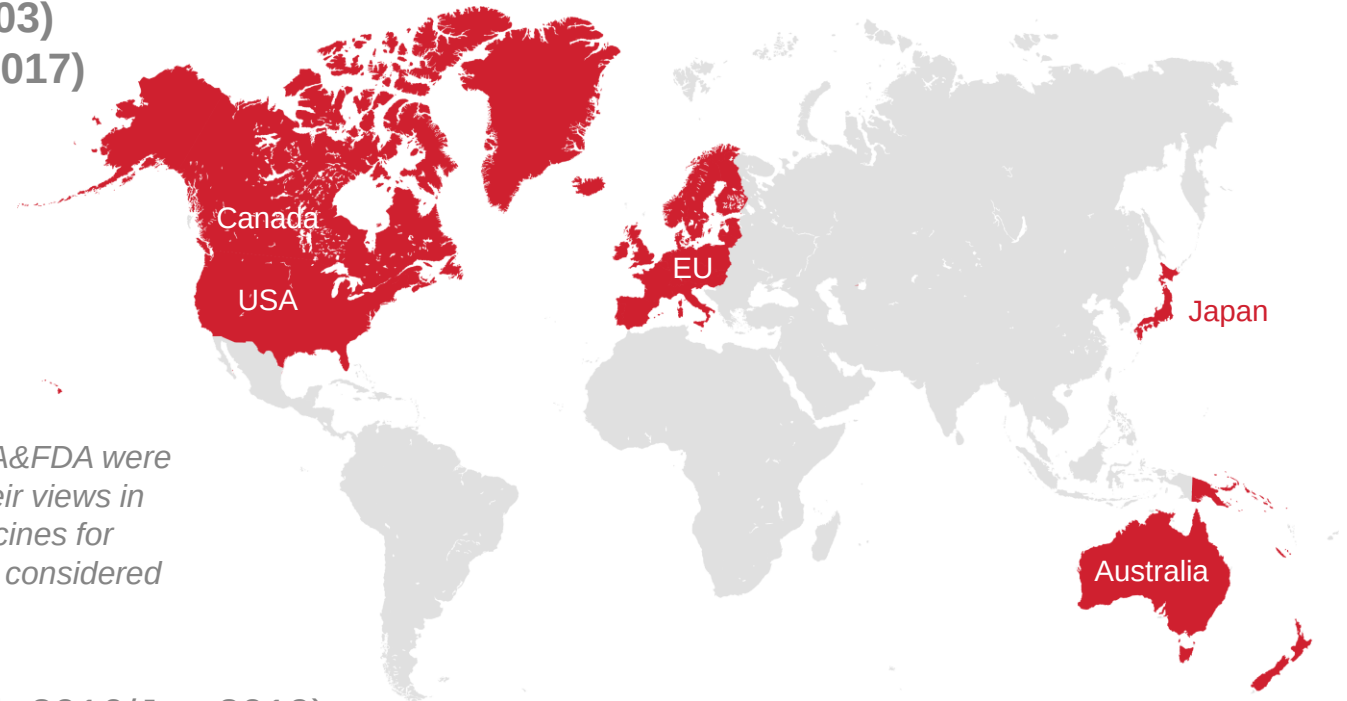
- EU Pediatric Regulation (2007) – Regulation (EC) No 1901/2006 as amended

■ Following Closely

- | | | |
|--|--------------------------------------|--|
| <ul style="list-style-type: none">■ Canada■ Australia■ Japan | } FDA-EMA Monthly Cluster Meetings } | <i>In 2017, EMA&FDA were aligned in their views in 73% of medicines for children they considered</i> |
|--|--------------------------------------|--|

■ Switzerland

- Revision of Therapeutic Products Law (March 2016/Jan 2019):
Obligation to submit pediatric plans & financial incentives



Pediatric Regulations – Implications



- Pediatric rules mandate pediatric drug development
 - Required for new medicines, new indications, new pharmaceutical forms, new routes of administration of existing authorized products, unless a waiver is granted



Pediatric drug development is no longer an option

Recent reinforcements of Pediatric Regulation - EU



■ EU reinforcement of the Pediatric Regulation (EC No 1901/2006 as amended)

■ Less class waivers since July 2018

- Classes of medicines that are likely unsafe or ineffective in children, lack benefit for pediatric patients or are for diseases and conditions that only affect adults

Will result in
more medicines
for children

■ List of pediatric medical needs

- Challenges seen in development of medicines for diseases that only affect children or for diseases that manifest differently in adults and children, hence the authorities will develop a list of pediatric needs to be available after 2020

Will result in the development
of more drugs specific for
children diseases, and
drugs for neonates

Recent reinforcements of Pediatric Regulations - US



- RACE (Research to Accelerate Cures and Equity) for Children Act - passed on Aug.3, 2017, applicable Aug.18, 2020

- Ends the exemption of PREA obligations for cancer drugs with orphan designations if the molecular target of their drug is relevant to a children's cancer
 - 205 candidate molecular targets for Pediatric Cancer Research & only 5 molecular targets for automatic waivers

Will result in more medicines for children having cancer

- “Pediatric Rare Disease Priority Review Voucher” program

- Re-authorized by Congress in the 21st Century Cures Act, extending the program **through September 2020**

Important incentive to encourage the development of medicines for pediatric rare diseases

Priority Review Voucher - Transactions



- Examples of Transactions for Priority Review Vouchers

Recipient	Product	Year	Acquiror	Price
BioMarin	Vimizim	2014	Regeneron, Sanofi	\$67.5M
Knight	Impavido	2014	Gilead	\$125M
Asklepion (Retrophin)	Cholbam	2015	Sanofi	\$245M
United Therapeutics	Unituxin	2015	Abbvie	\$350M
Sarepta Therapeutics	Exondys 51	2017	Gilead	\$125M

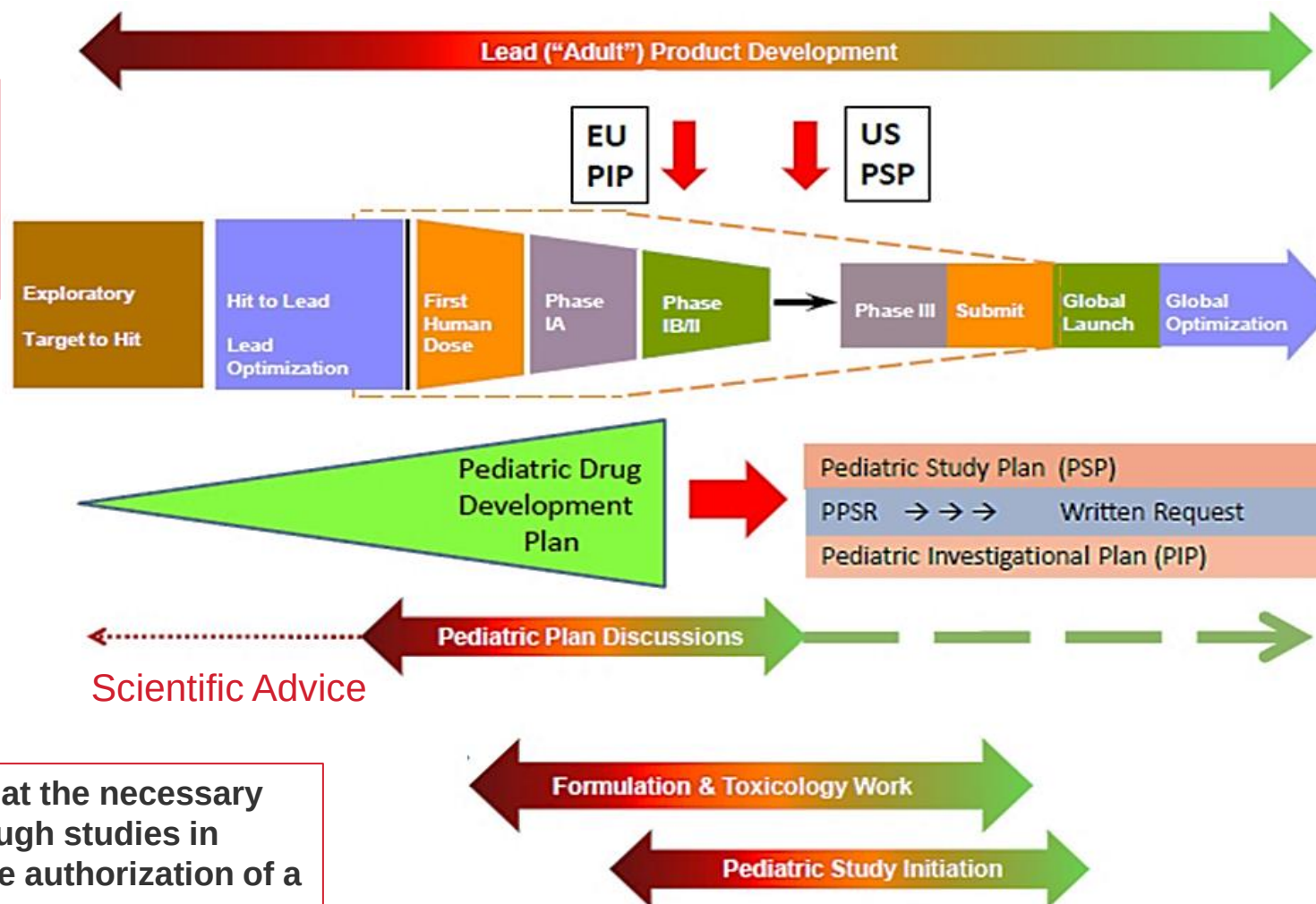
Pediatric Study Plans: Timing

EU (PIP)

- Availability of PK Data in adults
- End Phase 1

USA (iPSP)

- End Phase 2
- 60 Days EOP2 Meeting



PSP/PIP – to ensure that the necessary data are obtained through studies in children, to support the authorization of a medicine for children

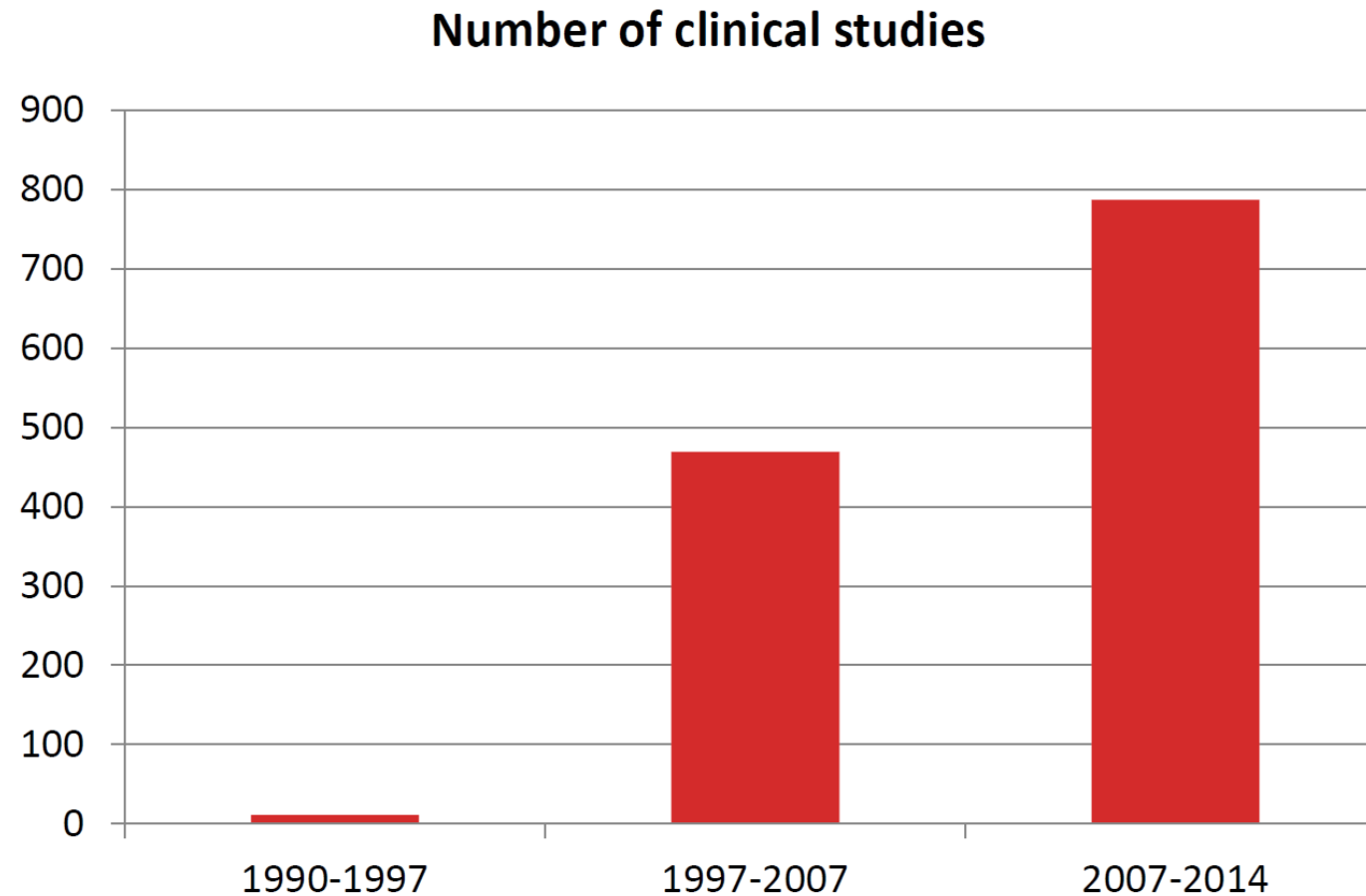


Present Day Success of Pediatric Regulations

Pediatric Regulations US – Impact on Clinical Trials



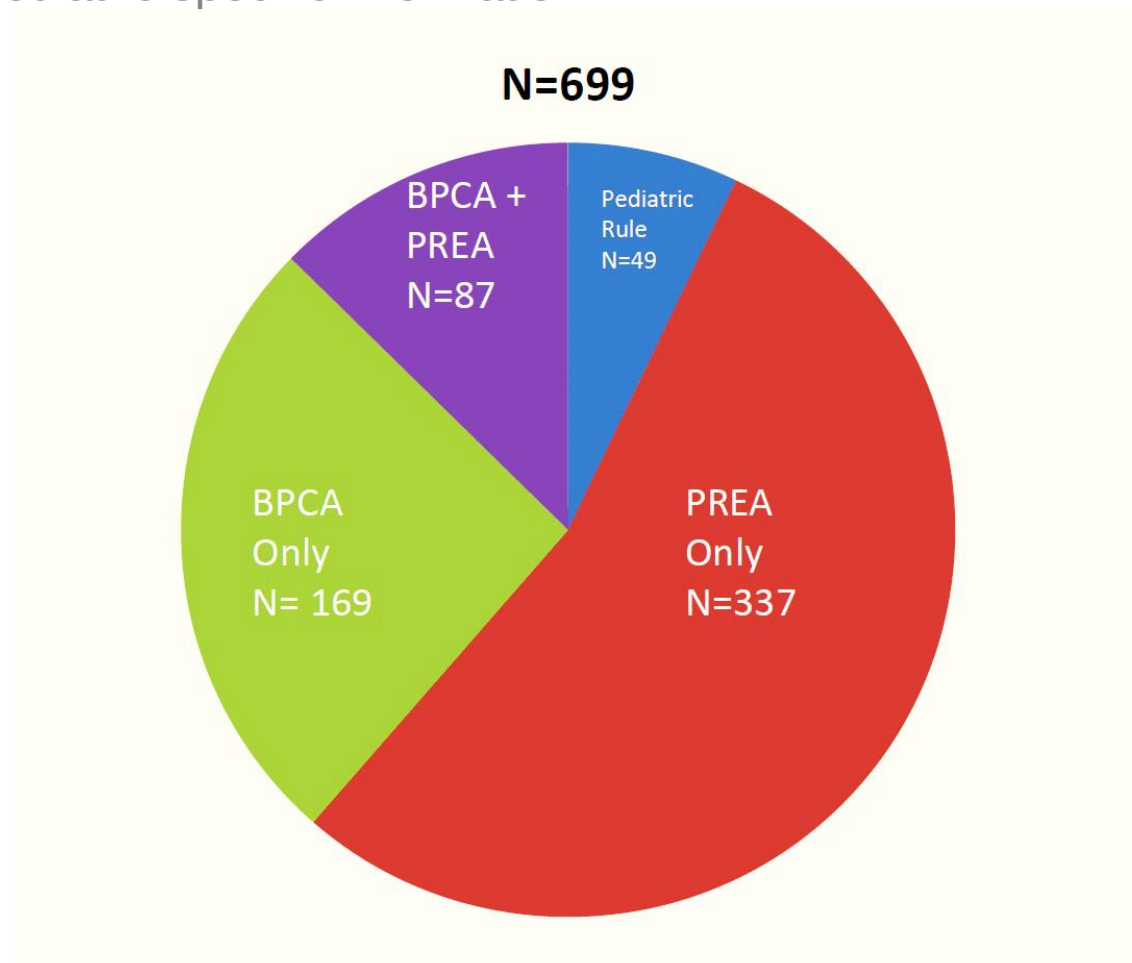
- Number Clinical Trials performed under BPCA and PREA



Regulations US – Impact on Pediatric Labeling



- Pediatric Labeling Changes 1998-2017
 - Incorporation of pediatric specific information

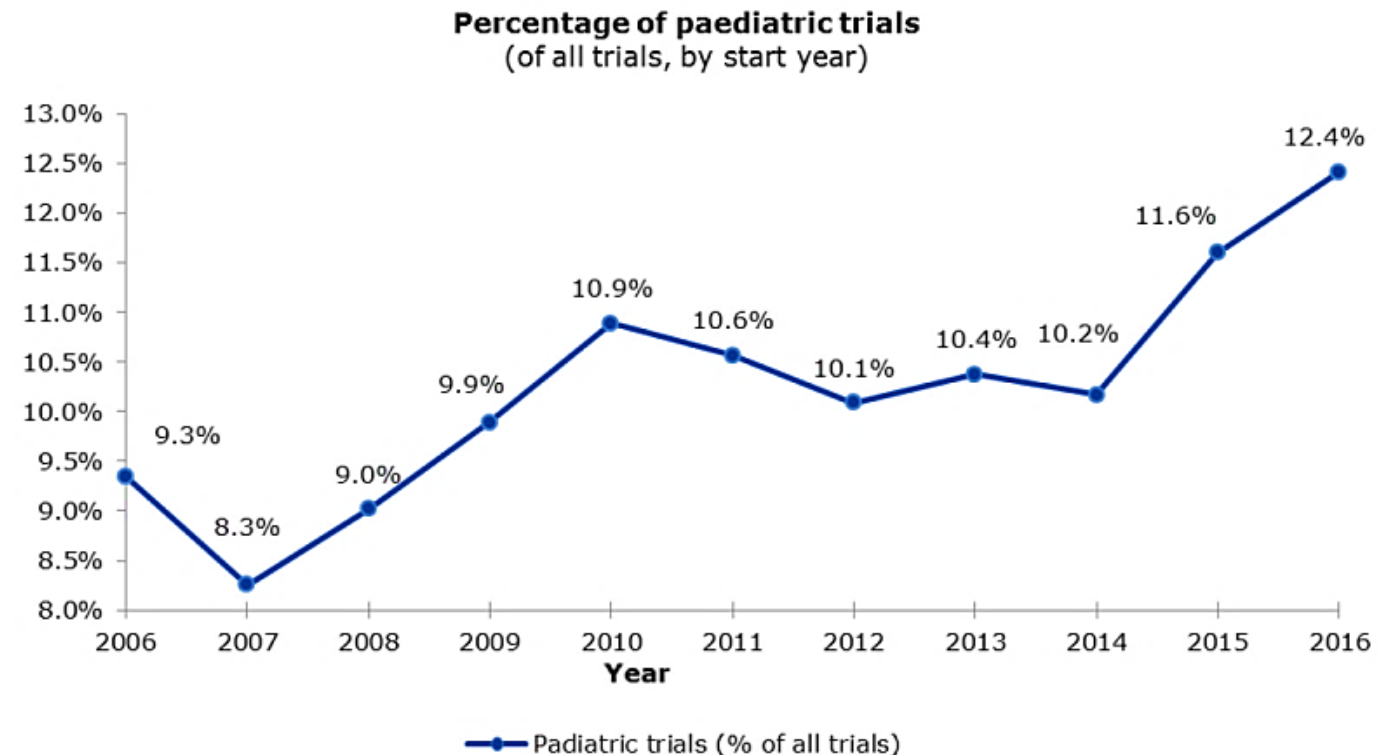


Pediatric Regulation EU – Impact on Trials



■ Increasing Number of Pediatric Trials

- 9.30 % of total trials in EU in 2006 up to 12.4% in 2016, i.e., 350-400 trials/year



Note: A paediatric trial is a trial that includes at least one participant below 18 years of age.

Source: EudraCT database

Pediatric Regulation – Impact on Approvals for Pediatrics



- More Medicines for Children

New paediatric medicines and indications per region (2007-2015)

Region	Much earlier legislation				No paediatric legislation	
	EU	US	Japan	Canada		
New paediatric medicines	80	76	12	38		
New paediatric indications	141	173	38	107		
Total	221	249	50	145		

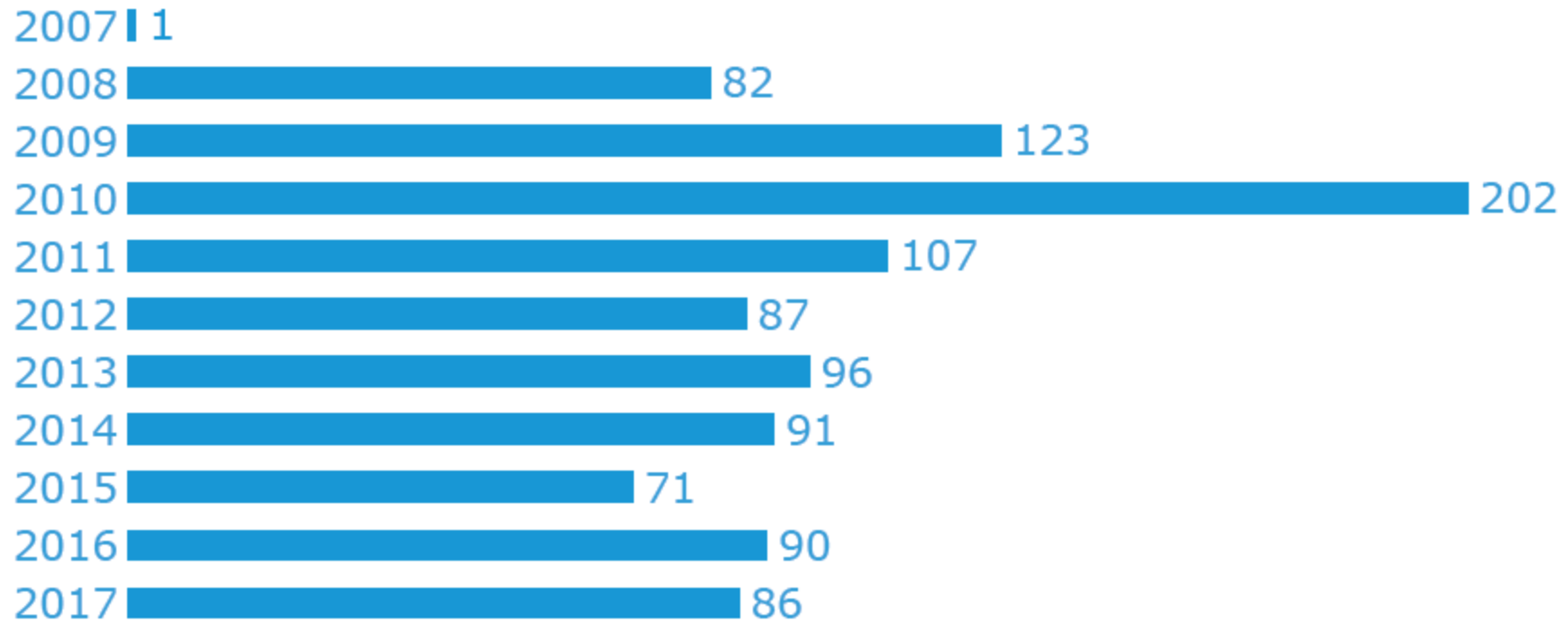
10-year report and Paediatric, D Mentzer 2017



EU – Number Agreed PIPs



PIPs agreed per year (2007–2017)





Challenges of Pediatric Regulation & Possible Solutions

Ten-Year Report of the European Commission (EC) on Implementation of the Pediatric Regulation



- **Success**

- Number of medicines developed for children increased

- **Specific challenges**

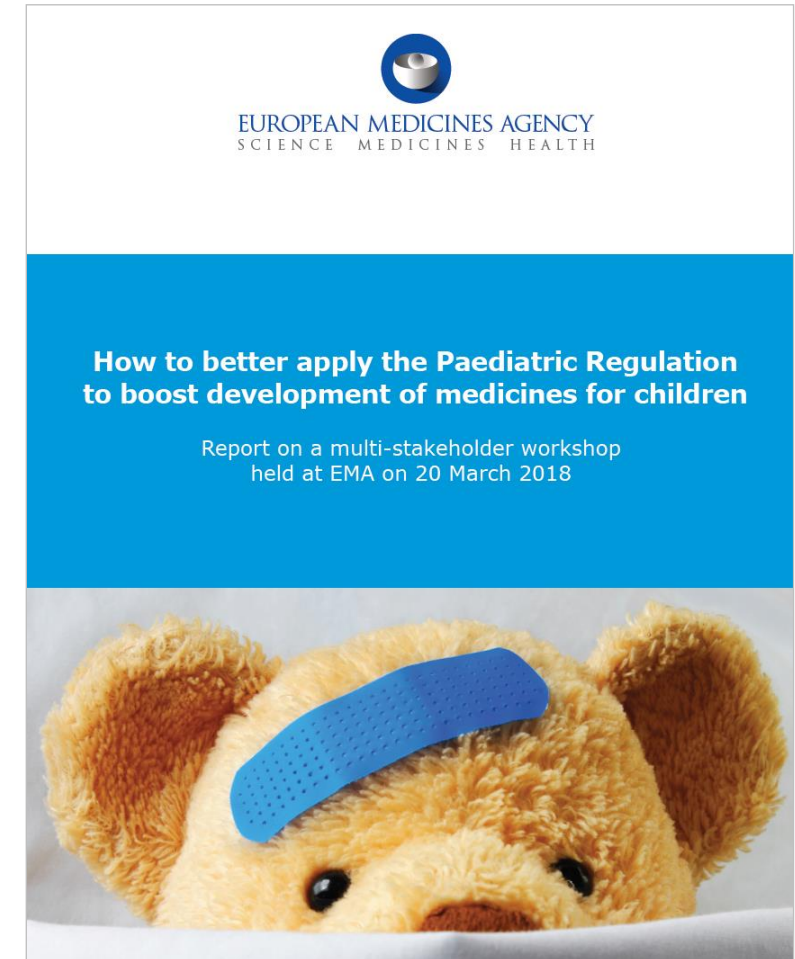
- In developing medicines for diseases that only affect children
 - In developing medicines for diseases with different manifestations in adults and children
 - In availability of pediatric medicines at the bedside as development and availability is often delayed when compared with adults medicines

- **Actions taken**

- Based on the analysis of the report, the European Commission (EC) and EMA committed to develop a detailed plan to boost the development of medicines for children, in consultation with all relevant stakeholders

How to Better Apply the Pediatric Regulation and Boost Development of Medicines for Children

- Stakeholder meeting at EMA on 20 March 2018
 - EC, EMA, patients & caregivers, academics, health care professionals, pharmaceutical industry
- Five topic areas discussed
 - Identifying pediatric medical needs
 - Strengthening of cooperation of decision makers
 - Ensuring timely completion of PIPs
 - Improving the handling of PIP applications
 - Increasing the transparency around pediatric medicines
- Action plan from EC and EMA based on suggestions made in stakeholder meeting
 - Published 02 October 2018



How to Better Apply the Pediatric Regulation and Boost Development of Medicines for Children – Action Plan



European Medicines Agency and European Commission
(DG Health and Food Safety) action plan on paediatrics

■ Action plan timelines

- Initially completion within a 2-years timeframe
- Due to impact Brexit & EMA relocation some actions are not expected to be completed by end 2020

■ Actions by topic area (21 actions in total)

1. Identifying paediatric medical needs

Action	Objectives	Status (July 2018)	Deadline	
3	Establish framework for collaboration of EMA/PDCO with the U.S. FDA's Oncology Center of Excellence Pediatric Oncology Program regarding the assessment of relevant molecular targets in paediatric cancers.	To maximise synergies and share expertise in the assessment of relevant molecular targets and to address medical needs with a global perspective.	In progress.	12/2019

2. Strengthening of cooperation of decision makers

3	Increase transparency with regard to EMA/FDA paediatric cluster discussions.	To better inform sponsors about paediatric cluster discussions and to increase transparency for all relevant stakeholders regarding outcomes of non-product related interactions.	In progress.	06/2020
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3. Ensuring timely completion of paediatric investigation plans (PIPs)

1	Publish recommendations to support the conduct of paediatric clinical trials.	To facilitate the conduct of paediatric clinical trials by focusing on identification and resolution of factors impeding the conduct of trials in children.	In progress.	12/2020
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4. Improving the handling of PIP applications

Action		Objectives	Status (July 2018)	Deadline
1	Explore possibilities for a PIP model that allows, in certain cases, for changes to be made to PIPs as more evidence becomes available over time.	To identify possibilities for and limitations of a PIP model that allows to develop along with the evolution of scientific knowledge.	In progress.	12/2020

5. Increasing transparency around paediatric medicines

Action		Objectives	Status (July 2018)	Deadline
1	Update Community Register of medicinal products with paediatric information (e.g. link to PIP information).	To facilitate the identification of medicinal products for which a PIP has been agreed and conducted.	Planned.	12/2020



Specificities of Pediatric Clinical Trials

Pediatric Clinical Trials: Ethical Considerations (1/2)



- Pediatric patients are considered **vulnerable** persons
- Children should only be enrolled in research if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally (i.e., adults)
- Adequate provisions to be made for soliciting the **assent** of the children and the **consent** of their parents or legal guardians
- Children should not be placed at a disadvantage by being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care

Pediatric Clinical Trials: Ethical Considerations (2/2)



- In the absence of direct clinical benefit, **risks and burden** must be “**minimal**” in comparison to standard treatment or “minor increase over minimal”
 - Placebo risk itself may be “minimal” unless invasive (e.g. injections)
 - Risks from withholding “proven” or “known effective” treatment
 - Placement of an indwelling port or central catheter in a patient receiving placebo would exceed “minor increase over minimal risk” (21 CFR 50.53)
 - Important to involve children in the assessment and minimisation of burden (Ethic Guidance 18 Sept.2017)

Ethical considerations for clinical trials on medicinal products conducted with minors

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

Revision 1

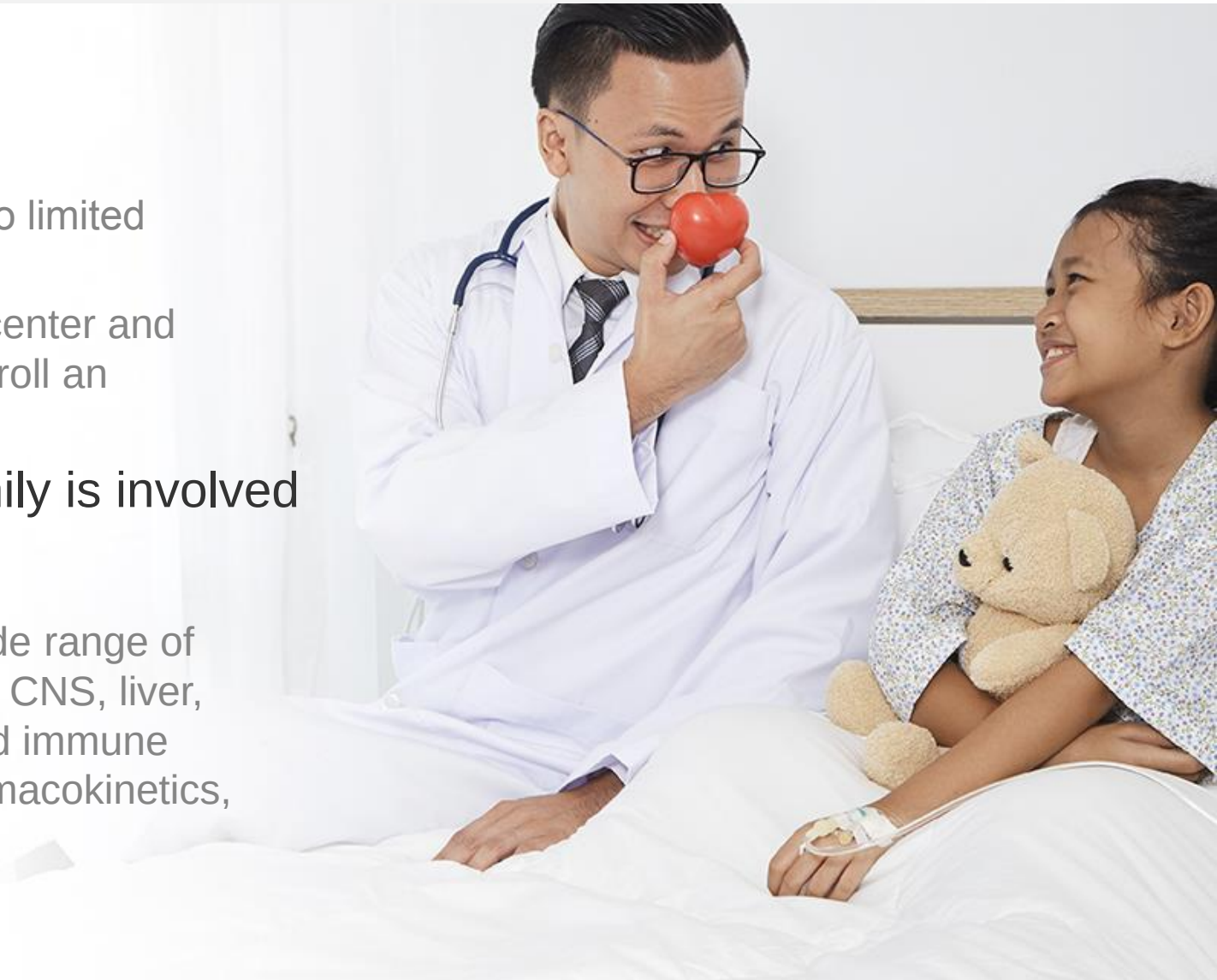
18 September 2017

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area

Specificities of Pediatric Trials



- **Limited patient population**
 - Children tend to be healthier
 - Children's illnesses tend to be acute so limited chronic patient population to study
 - Small populations which implies multicenter and often international/global studies to enroll an adequate number of patients
- **Not only the child but the entire family is involved**
- **Many age subsets**
 - Birth through adolescence spans a wide range of organ developmental maturation (e.g., CNS, liver, kidney, lung, skeletal, reproductive and immune systems), which may affect drug pharmacokinetics, efficacy and safety



Further Considerations for Pediatric Trials



- Juvenile Toxicity: Juvenile animal studies may be needed prior to conduct of pediatric trials
- Formulation: Age-appropriate pediatric formulations to assure accurate dosing. Safety of excipients must be considered
- Pediatric endpoints & assessment tools: Age-appropriate & validated (might be lacking or limited)
- PK: Sparse sample designs and application of modeling/simulation
- Effects of therapy: Chronic effects on growth, cognitive and sexual development of pediatric patients is to be evaluated
- Extrapolation:
 - If course of disease and effects of the drug are sufficiently similar in adult and pediatric patients, pediatric **efficacy** can be extrapolated from adequate and well- controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies
 - A study may not be needed in each pediatric age group if **efficacy** data from one age group can be extrapolated to another age group

Informed Consent - Process

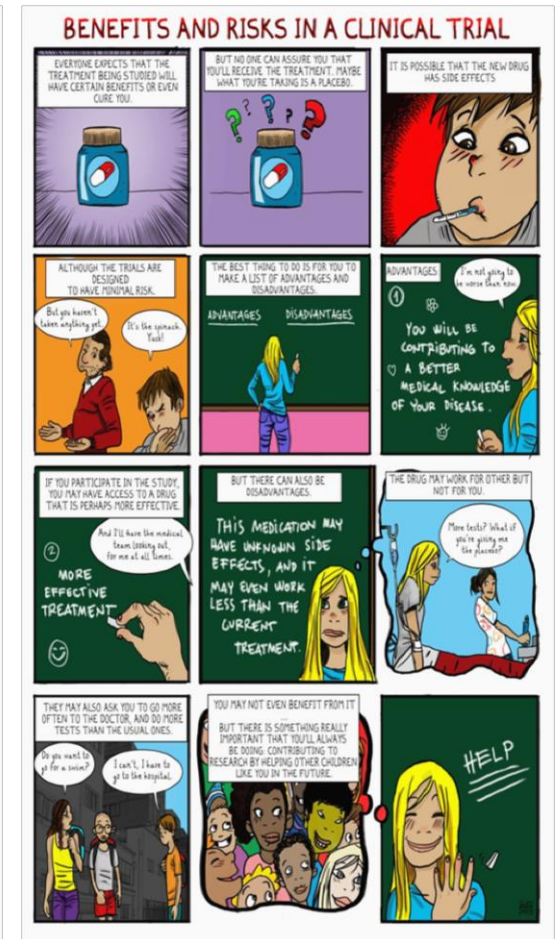


- Informed consent must be obtained from the child's legal representative
 - Parent, guardian or other legally recognised person as defined by national laws
- Parent/legal representative must
 - Have adequate time to consider the information provided and the risks and benefits to the child
 - Be placed under no undue pressure by the researcher
- No financial inducements should be offered
 - Except compensation for expenses and time spent
- First approach to be performed by experienced investigators



Assents

- Children are to be informed on
 - The purpose of the study
 - What will be done to them
 - The potential risks and benefits
 - The voluntary nature of participation and freely withdraw possibility at any time for any reason, without any disadvantage or prejudice
- Age Appropriate language
- Assent Form per age group
 - Age groups not harmonized among countries
 - State and IRBs dependent in US



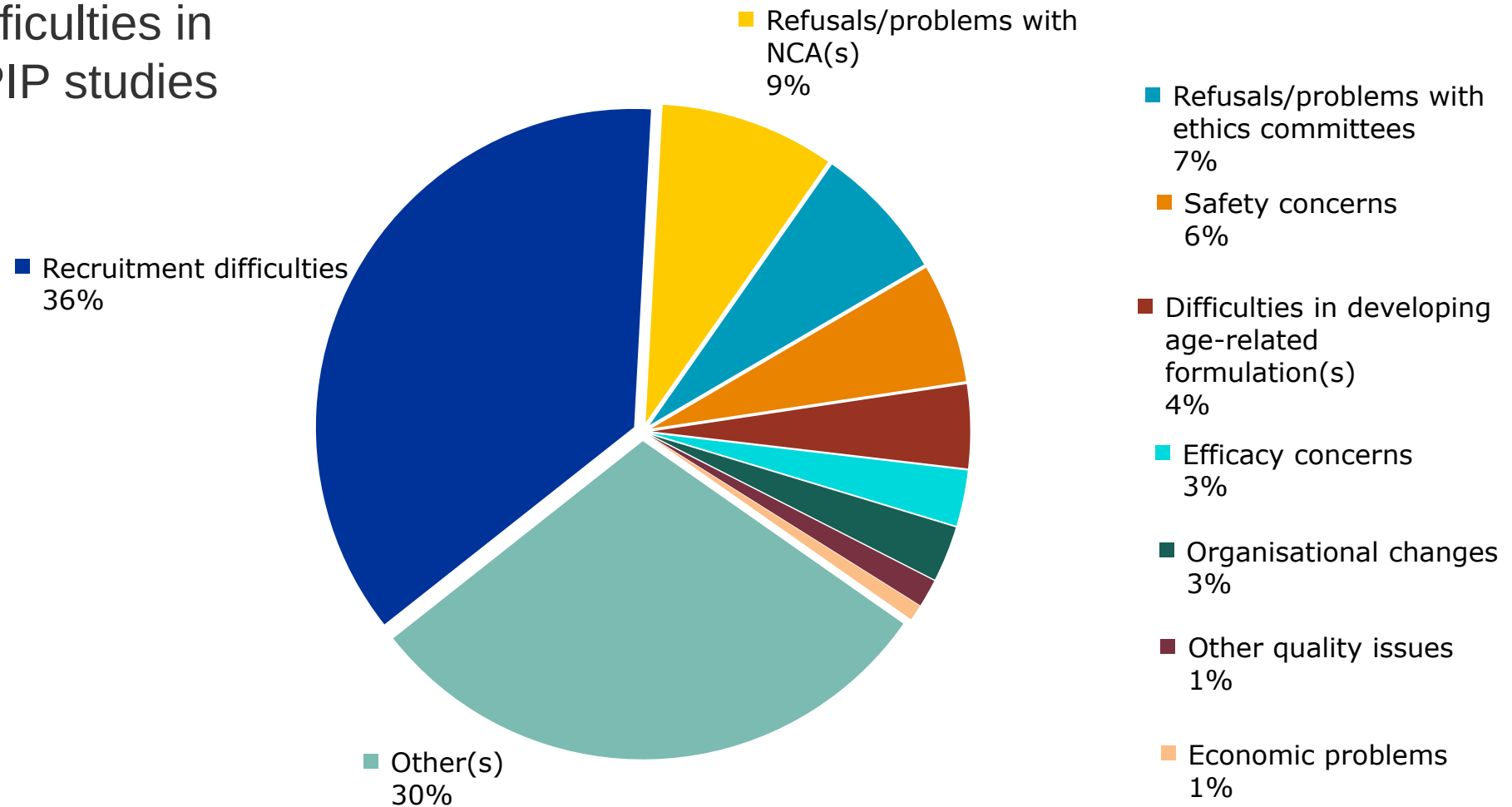


Key Considerations for Successful Pediatric Trials

Main challenges in Pediatric Studies as per Reports to EMA



■ Reported difficulties in conducted PIP studies



Source: EMA, 12 Oct. 2016

How to assure Successful Pediatric Trials – Adequate Sites



- Performing trials at the most appropriate sites
 - Pediatric site networks
 - Institute For Advanced Clinical Trials For Children – IACT
 - European Network of Pediatric Research at EMA – Enpr-EMA
 - Network of research networks, investigators and centres with recognised expertise in performing clinical studies in children
 - Enpr-EMA facilitates pediatric trials by
 - fostering high-quality, ethical research on the quality, safety and efficacy of medicines for use in children;
 - helping with the recruitment of patients for clinical trials;
 - enabling collaboration between networks and stakeholders;
 - avoiding unnecessary duplication of studies;
 - building up scientific and administrative competence at a European level;
 - promoting European Commission framework program applications.
 - Enpr-EMA Database with over 40 pediatric networks



Future Pan European Pediatric Network



■ Conect4children - c4c

- **c4c** is a large collaborative **European network** that aims to
 - facilitate development of new drugs & therapies for pediatric population
- c4c is committed to meeting the needs of pediatric patients thanks to a novel collaboration between the academic and the private sectors
 - 33 academic & 10 industry partners
 - 20 European countries
 - over 50 third parties and around 500 affiliated partners
- c4c endeavours to provide
 - a sustainable, integrated platform
 - efficient and swift delivery of high quality clinical trials in pediatrics
 - supports for all conditions and phases of the drug development
- IMI2 Project – Launched in 2018 - Six year project – Euro 140 Mio
- Pilot Phase: 7-8 trials - 4 academic trials and 3-4 industry trials, covering different diseases and age groups



How to Ensure Successful Pediatric Trials – Patient Centricity



■ Requirements

- Clinical Trials Regulation EU No 536/2014 & Ethic Guidance Minors (18 Sept. 2017)
 - Protocol to include “description of patients involvement in trial design”. Justification of exception of recommendation
- FDA 21st Century Cures and PDUFA VI
 - FDA Patient-Focused Drug Development

■ Patients/Children involvement in

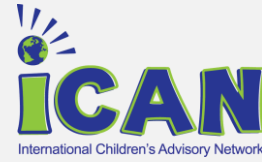
- Pediatric research, protocol design, patient facing documents review

■ Children Advisory Groups

- iCAN, the International Children’s Advisory Network
- eYPAGNet, European Young Persons’ Advisory Group Network



iCAN - Annual Summits



2019 – Kansas City, USA



2018 – Scotland, UK



Conclusion

Conclusion



Pediatric development is no longer an add-on but an integral part of the drug development process

Global regulations are driving pediatric drug development

Regulator and stakeholder collaboration to improve global pediatric research

Pediatric trials have unique specificities which are to be considered for optimal trial set up and execution

Collaboration of all stakeholders will lead to more pediatric medicines developed and available to treat children



THANK YOU FOR YOUR ATTENTION

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