

International Considerations for Pediatric Master Protocols

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Disclaimer

- **I have no Conflicts of Interest**
- **The opinions expressed are entirely mine and do not reflect any official FDA statement.**

Pediatric Trials Are Unique

- **Pediatric Legislation in the US and EU is driving the conduct of pediatric studies on a global scale**
 - Need to harmonize the conduct of these studies
- **Limited pediatric population with a given disease or condition available for study**
 - Pediatric studies often global, involving many centers and countries
 - Maximize information obtained in the study

Pediatric Trials Are Unique

- **An approach to maximize prior knowledge: Extrapolation of Efficacy**
 - **Consider extrapolation of efficacy from adequate and well-controlled adult studies if**
 - **course of disease AND expected response to therapy are sufficiently similar between adult and pediatric patients. This is unique to pediatrics.**
 - **Still need to obtain pediatric PK and safety data. PK and thus, dosing, can differ from adults or among various pediatric age groups. Also, children may have adverse events that differ from adults or that occur with a higher frequency or are more serious.**
 - **Consider conduct of multi-agent, multi-company trials (e.g. Gaucher disease)**
- **Not only limited pediatric patient population but limited blood volume, particularly in neonates and infants**
 - **Sparse sampling with population PK and use of modeling and simulation; unique to pediatrics**

Pediatric Trials Are Unique

- **Many age subsets require studies, not just one study covers all of pediatrics**
 - **Sequential approach by pediatric age- from oldest to youngest- may be implemented to understand dosing and safety before studying next youngest age cohort**
- **The disease may occur only in specific pediatric age subset(s)**
- **Science may be lacking to design the needed studies**
 - **Example: need age-appropriate and validated endpoints and assessment tools**
- **Need infrastructure (facilities, equipment, laboratories) and pediatric scientific and ethical expertise. Need pediatric trials networks.**
- **Need age-appropriate formulations for accurate and safe dosing. Issue of excipients particularly in neonates and infants.**

Pediatric Trials Are Unique

- **Need to provide children with additional ethical protections**
- **Challenge to obtain long-term follow-up studies to assess effects on growth, cognitive and sexual development and to address product or class specific safety concerns**
 - e.g. conduct open-label extensions of randomized trials or establishment of registries
- **May need juvenile animal studies prior to pediatric studies**
- **Study of pediatric patients with rare diseases and study of neonates: unique challenges but most understudied patient populations**
- **Understand why pediatric trial failed so can inform design of future trials**
 - e.g. faulty study design or incorrect dose studied

Critical Role of Pediatric Global Collaboration

- **With pediatric legislation in the US and EU driving pediatric product development on a global scale, it is critical to harmonize product development to the extent possible.**
- **Children must not become a commodity to earn the regulatory incentive that exists in the U.S. and European Union.**
- **Avoid conduct of unnecessary and duplicative trials. Enroll children only in trials that answer a needed scientific question and that are ethically conducted.**

Challenges to Harmonization

- **Different pediatric legal frameworks and processes**
 - **Pediatric Requirement and the Incentive**
 - **US: separate legislations, processes and timelines for requirement (mandatory) and incentive (voluntary). Therefore, in the US, pediatric exclusivity is a **SEPARATE** process.**
 - **EU: unified process for requirement and incentive. Hence, no voluntary component.**
- **Scope of the pediatric legislative requirements**
 - **US: requirement linked to adult indication**
 - **EU: linked to “condition”: broadly interpreted**
- **Exemptions from the pediatric legislative requirement**
 - **Orphan products: exempt in US but not in EU**
 - **Biosimilar products: exempt in EU but not US**

Challenges to Harmonization

- **Timing differences for submission of pediatric plan**
 - US: within 60 calendar days of EOP2 meeting
 - EU: EOP1 in adults
 - Timing differences: mostly resolved as timelines have moved closer between the two Agencies
 - **Modifications to an agreed pediatric plan**
 - US: FDA can modify at any time as necessary
 - EU: EMA cannot modify once a final opinion is rendered, only the sponsor can initiate the change.
 - **Resource/organizational structure differences**
 - **Cultural differences**
 - **Differences in scientific practices & standards of care**
- DESPITE THESE DIFFERENCES...**

Shared Common Goal

- **Timely, ethical and sound scientific development of products in the pediatric population with the objective of labeling them for safe and effective use.**
- **To do this, we must work together.**



Achieving a Global Pediatric Approach

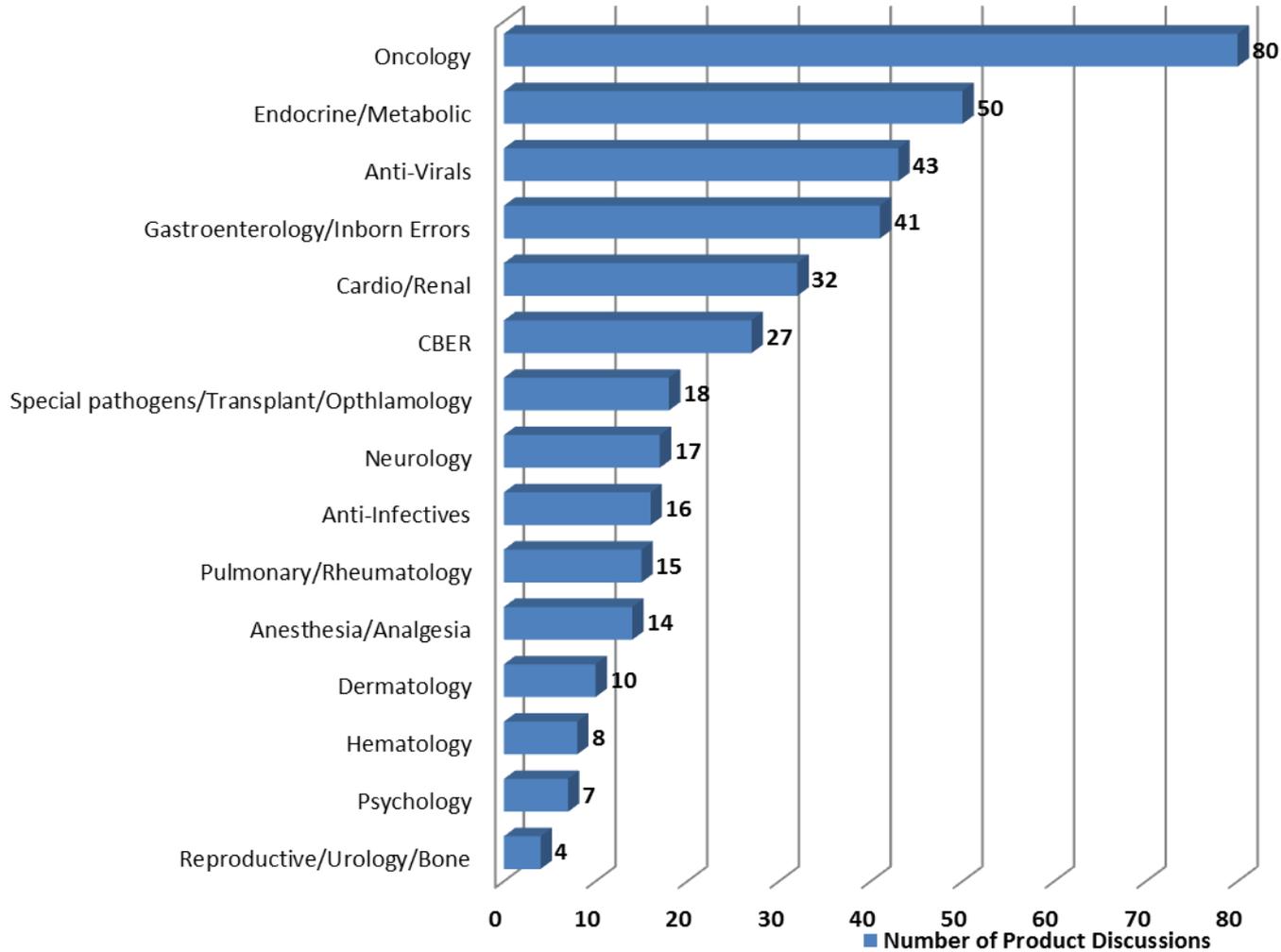
- **Ongoing harmonization of the science is the most useful and productive approach. This will make pediatric product development easier and faster.**
 - **Pediatric Cluster teleconferences**
 - **Joint Working Groups, Workshops and Expert Meetings for extended discussions**
 - **Joint Publications**
 - **Global Pediatric Trials Networks and Consortia**

Pediatric Cluster

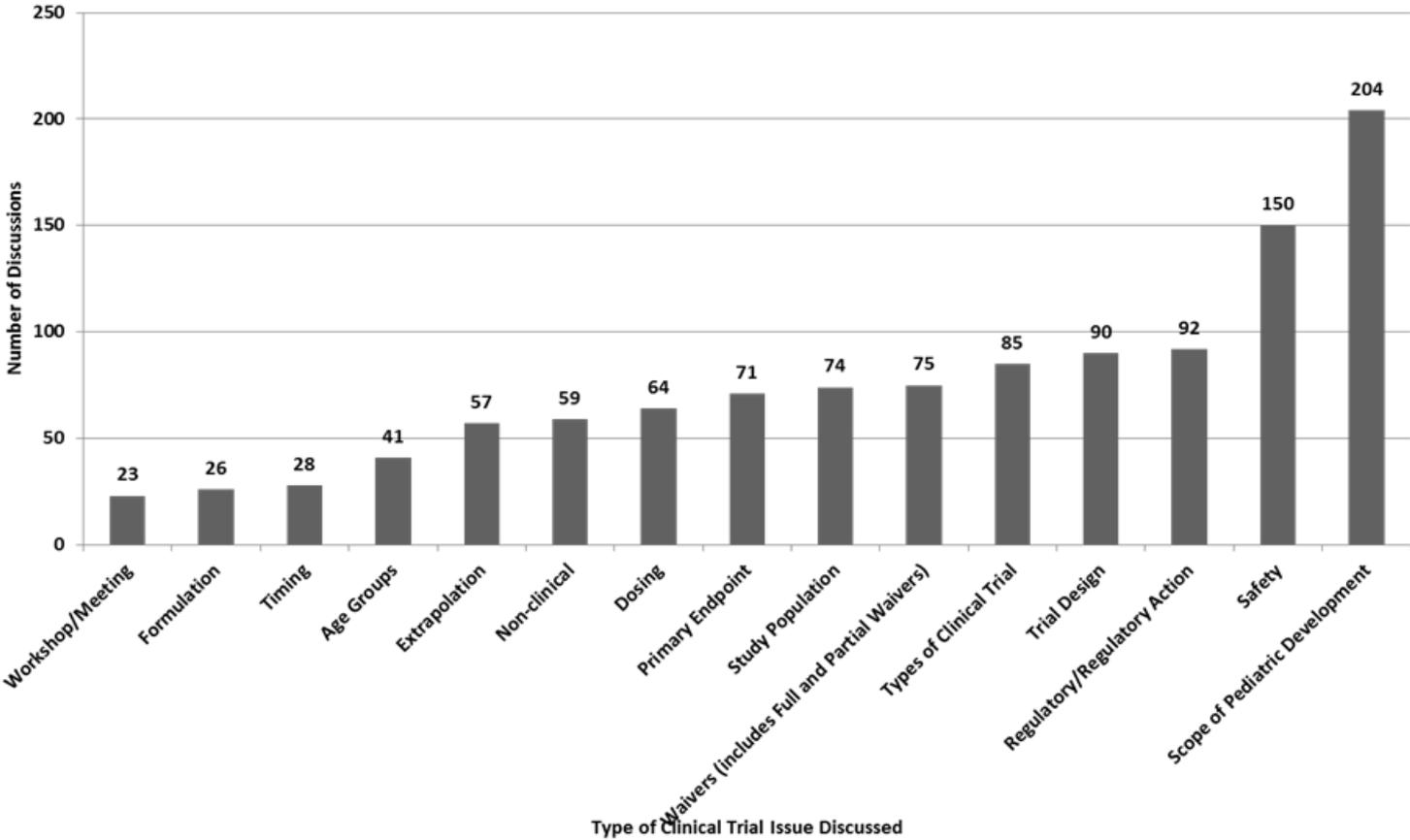
- **Established in 2007**
- **At least monthly informal discussions between regulators, which currently includes FDA, EMA, Health Canada, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and Australia's Therapeutic Goods Administration (TGA).**
- **Since 2007, 417 products and 136 general topics (e.g. safety concerns pertaining to a product class) have been discussed in 106 teleconferences.**
- **Frequently discussed product issues include scope of pediatric product development, safety, trial design and endpoints.**
- **Convergence on approaches has been achieved for 73% of the issues discussed in the past 3 years.**

Pediatric Cluster Products Discussed by Division 2007-2015

n=382



Frequency of Clinical Trials Issues Discussed at Pediatric Cluster 2007-2015



Joint Pediatric Working Groups

- **Examples: IBD WGs for pediatric ulcerative colitis & Crohn's disease**
- **Need global approach: multiple products in pipeline, limited patients**
- **Participants: FDA, EMA, Health Canada and Japan's PMDA**
- **Issues: extrapolation/dose-finding/study design/endpoints/biomarkers**
- **Outcome:**
 - **Publication of 3 joint manuscripts**
 - **"Steps Toward Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis- a Global Scientific Discussion Part 1: Efficacy Endpoints and Disease Outcome Assessments" *JPGN* 2014 Jan 9.**
 - **"Steps Towards Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis- Global Scientific Discussion Part 2: Data Extrapolation, Trial Design, and Pharmacokinetics" *JPGN* 2014 Jan 23.**
 - **"Pediatric Crohn's Disease Clinical Outcome Assessments and Biomarkers: Current State and Path Forward for Global Collaboration" accepted for publication *JPGN* 2016 May 18**

Additional Joint Pediatric Working Groups

- **EMA's Nonclinical WG includes FDA representation**
- **EMA's Formulations WG includes FDA representation**
- **Additional joint pediatric WGs, which may be disease-specific, will be established on an ad hoc basis when extended in-depth discussions are needed and they will be an extension of the Pediatric Cluster.**

Joint Pediatric Workshops

- **Example: Gaucher Disease Workshop in September 2012**
- **Global strategy imperative in this orphan disease and with multiple products in the pipeline**
- **Participants: FDA, EMA, industry, experts and patient organizations**
- **Issues: extrapolation; endpoints; multi-arm, multi-company trials**
- **Outcome: FDA and EMA website posting: “Gaucher Disease A Strategic Collaborative Approach from EMA and FDA”**
- **Public comments received and under review**

Additional Joint Pediatric Workshops and Expert Meetings

- **Advancing the Development of Pediatric Therapeutics (ADEPT)**
 - **Coordination by FDA**
 - **Participation: regulators, academicians, investigators, industry, patient advocacy groups**
 - **ADEPT 1: Pediatric Bone Health on June 3, 2014**
 - **ADEPT 2: Evaluation of Long-term Neurocognitive Development in Pediatrics on April 17, 2015**
 - **ADEPT 3: Successes and Challenges of Performing Long-term Pediatric Safety Studies on April 13-14, 2016**
- **EMA expert meetings in conjunction with FDA**
 - **e.g. diabetes, HIV, rheumatology and osteoporosis**

Joint Publications

- 1) **Gaucher disease : A strategic collaborative approach from EMA and FDA (published on FDA and EMA websites May 2014)**

- 2) **Steps towards Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis—a Global Scientific Discussion. Part 1: Efficacy Endpoints and Disease Outcome Assessments** Haihao Sun, MD, PhD, Richard Vesely, MD, Jan Taminiiau, MD, Peter Sztanyai, MD, Maria Isaac, MD, Agnes Klein, MD, Shinobu Uzu, Donna Griebel, MD, Andrew E. Mulberg, MD on behalf of the International Inflammatory Bowel Disease (i-IBD) Working Group *Journal of Pediatric Gastroenterology & Nutrition* 2014 Jun 9 [Epub ahead of print]
http://journals.lww.com/jpgn/Abstract/publishahead/Steps_Towards_Harmonization_for_Clinical.98409.aspx

- 3) **3) Steps towards Harmonization for Clinical Development of Medicines in Pediatric Ulcerative Colitis – a Global Scientific Discussion.**
Part 2: Data Extrapolation, Trial Design, and Pharmacokinetics Haihao Sun, MD, PhD, Richard Vesely, MD, Robert M Nelson, MD, PhD, Jan Taminiiau, MD, Peter Sztanyai, MD, Maria Isaac, MD, Agnes Klein, MD, Shinobu Uzu, Donna Griebel, MD, and Andrew E. Mulberg, MD on behalf of the international Inflammatory Bowel disease (i-IBD) Working Group *Journal of Pediatric Gastroenterology & Nutrition* 2014 June 23 [Epub ahead of print]
http://journals.lww.com/jpgn/Abstract/publishahead/Steps_towards_Harmonization_for_Clinical.98391.aspx

- 4) **Joining Forces: A Call for Greater Collaboration To Study New Medicines in Children and Adolescents with Type 2 Diabetes** Janina Karres PhD, Valerie Pratt MD, Jean-Marc Guettier MD, Jean Temeck MD, William V. Tamborlane MD, David Dunger MD PhD, Cristina Bejnariu MD¹, Carine DeBeaufort MD PhD, Paolo Tomasi MD PhD *Diabetes Care* October 2014; 37: 2665

Joint Publications

5) A Comparative Review of Waivers Granted in Pediatric Drug Development by FDA and EMA from 2007-2013 Gunter F. Egger, DVM^{†a}, Gerold T. Wharton, MS^b, Suzanne Malli, BA, BSN^b, Jean Temeck, MD^b, M. Dianne Murphy, MD^b, Paolo Tomasi, MD, PhD
Therapeutic Innovation & Regulatory Science, 1-9 May 2016

6) Pediatric Crohn's Disease Clinical Outcome Assessments and Biomarkers: Current State and Path Forward for Global Collaboration H Sun, R Vesely, A Klein, M Ikima, AE Mulberg, International Inflammatory Bowel Disease (i-IBD) Working Group J
Pediatr Gastroenterol Nutr 2016 June 2 [Epub ahead of print]

7) Impact of the Food and Drug Administration (FDA)-European Medicines Agency (EMA) Common Commentary (CC) on Pediatric Cancer Development G Reaman, R Herold, K Norga, M Donoghue, D Casey, M Chuk, P Dinndorf, J Leighton, J Sterba, P Paolucci, P Baiardi, H van den Berg, J Carleer, J Temeck, S Malli, D Murphy *Poster accepted for the 48th Congress of the International Society of Paediatric Oncology October 19-22, 2016 in Dublin, Ireland*

International Pediatric Trials Networks

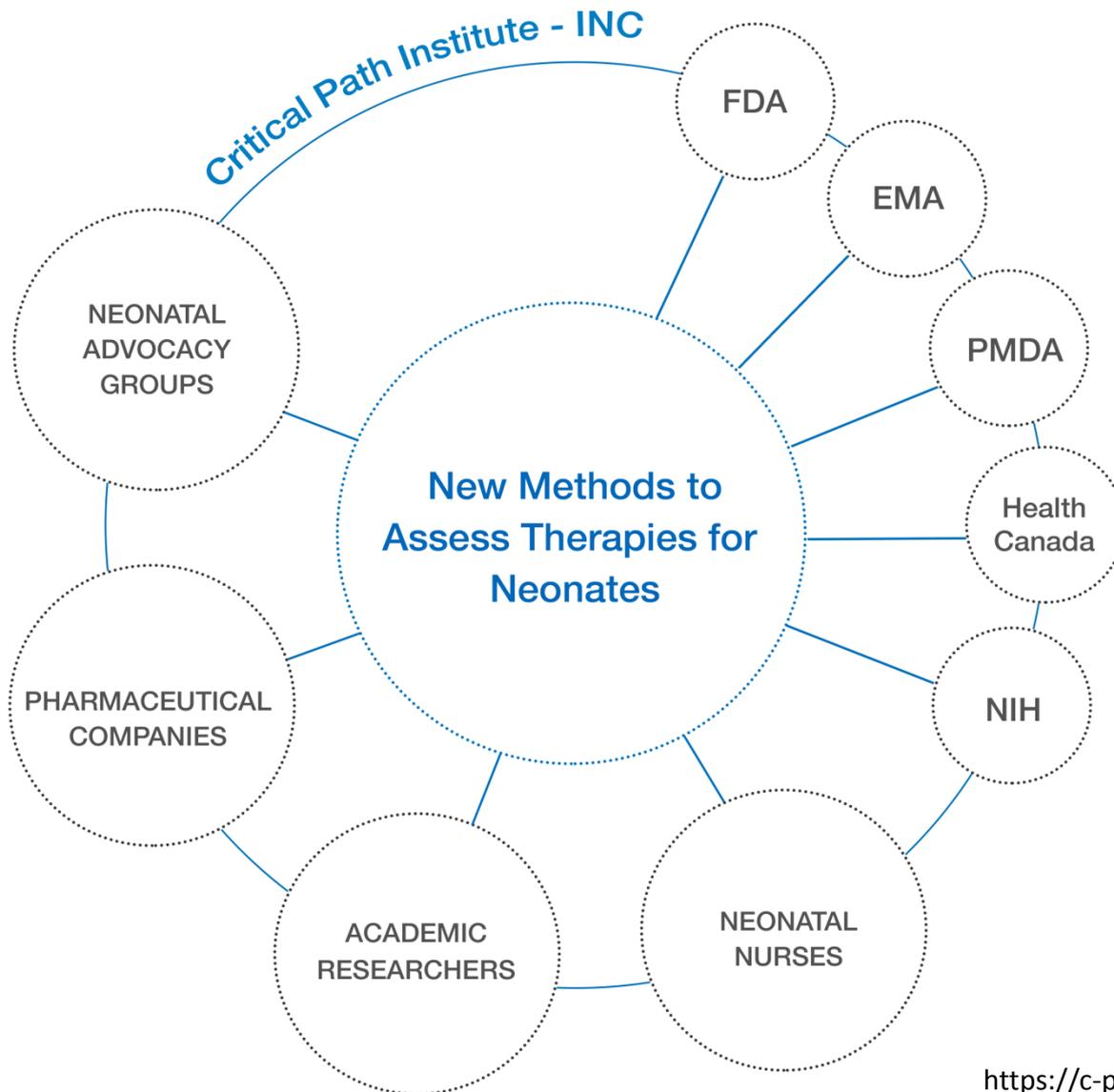
- **Will provide the global pediatric clinical research infrastructure needed to develop safe and effective therapies in children**
- **Public-Private Partnerships (academicians, clinicians, regulators, pharmaceutical industry and patient advocacy groups)**
- **International Neonatal Consortium**
- **Pediatric Trials Consortium**

International Neonatal Consortium (INC)

- Launched by the Critical Path Institute on May 19, 2015
- **MISSION**

Accelerate the development of safe and effective therapies in neonates. This consortium will engage the global neonatal community to focus on the needs of the neonate. Through teams that share data, knowledge and expertise, INC will advance medical innovation and regulatory science for this underserved population.

Members Spanning the Globe



Neonatal Nurses

- NANN
- COINN

Founding Companies

- AstraZeneca
- Janssen
- Lilly
- Novartis
- Pfizer
- Sanofi
- Shire

Families/Advocacy

- Graham's Foundation
- March of Dimes

Global Pediatric Clinical Trials Network

- **Landmark meeting in November 2014 hosted by the American Academy of Pediatrics (AAP). Shared vision to create and sustain an independent Global Pediatric Clinical Trials Network.**

- **VISION**

Facilitate development and availability of innovative, high-quality therapies to extend and enhance the lives of neonates, infants, children, adolescents and young adults.

Pediatric Trials Consortium (PTC)

- **Critical Path Institute implemented this vision by establishing the Pediatric Trials Consortium.**

- **MISSION**

Timely and efficient development and evaluation of innovative drugs, biologics and devices for children by delivering high-quality, reliable data to inform product labeling and, thus, treatment decisions by health care providers for their pediatric patients.

- **Focus: high-quality product development global clinical trials in the pediatric population that adhere to regulatory standards.**
- **Members span the globe (C-Path, AAP, DIA, academicians, clinicians, regulators, patient advocates, pharmaceutical companies).**
- **Launch this new independent, non-profit public-private partnership in early 2017.**



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International Collaborations

Humanitarian Use Devices and Humanitarian Device Exemption

Publications

Pediatric Presentations

Pediatrics



- [New Pediatric Labeling Information Database](#)
- [Safety Reporting Updates](#)
- [Pediatric Study Characteristics Database](#)
- [List of Exclusivity Determinations \(PDF - 179KB\)](#)
- [Medical, Statistical, and Pharmacology Reviews 7/9/2012- present](#)
- [Medical, Statistical and Pharmacology Reviews 9/2007- 7/2012](#)

Spotlight

- [Gaucher disease - A Strategic Collaborative Approach from EMA and FDA](#)
- [Public Workshop – Pediatric Clinical Investigator Training](#)
- [2014 Meeting Materials, Pediatric Advisory Committee to the FDA](#)
- [AAP News FDA Update](#)
- [FDA Pediatric Safety Communications](#)

About Us

- [Office of Pediatric Therapeutics](#)

Related Links

Conclusions

- **GLOBAL COLLABORATION**
 - Critical to ensure enrollment of children in scientifically and ethically sound trials that answer a needed question.



CONCLUSIONS

- **Pediatric Cluster, related working groups, and joint workshops and expert meetings are key to resolving many issues expeditiously.**
- **We converge approaches on many issues through the discussions, and publish jointly.**
- **Differences will remain nonetheless**
 - **due to differences in legislation (notably differences for addressing pediatric exclusivity); regulatory processes; timing; resource/organizational structure differences; cultural differences and differences in scientific practices and standards of care.**
- **We must look past barriers and continue to find solutions**
 - **For example, formation of public-private partnerships to establish global pediatric clinical research infrastructure and networks. Establishment of pediatric trials networks and consortiums and development of pediatric master protocols will facilitate the timely and efficient development of therapeutics for children.**

Conclusions

- **GLOBAL COLLABORATION**

- Critical and involves ALL stakeholders working together to move pediatric therapeutics forward and get the desperately needed studies done so that sick infants and children receive safe and effective medicines.



THANK YOU!