International Collaborations in Pediatrics: FDA and EMA growing together

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Disclaimer

- *I have no financial or other conflicts of interest of relevance to this topic*
- *"The opinions are mine and do not necessarily reflect the views of FDA"*

- *Thanks to my FDA pediatrics colleagues for their assistance and enthusiastic discussion of the issues*

Regulatory science and public health wither without light and air

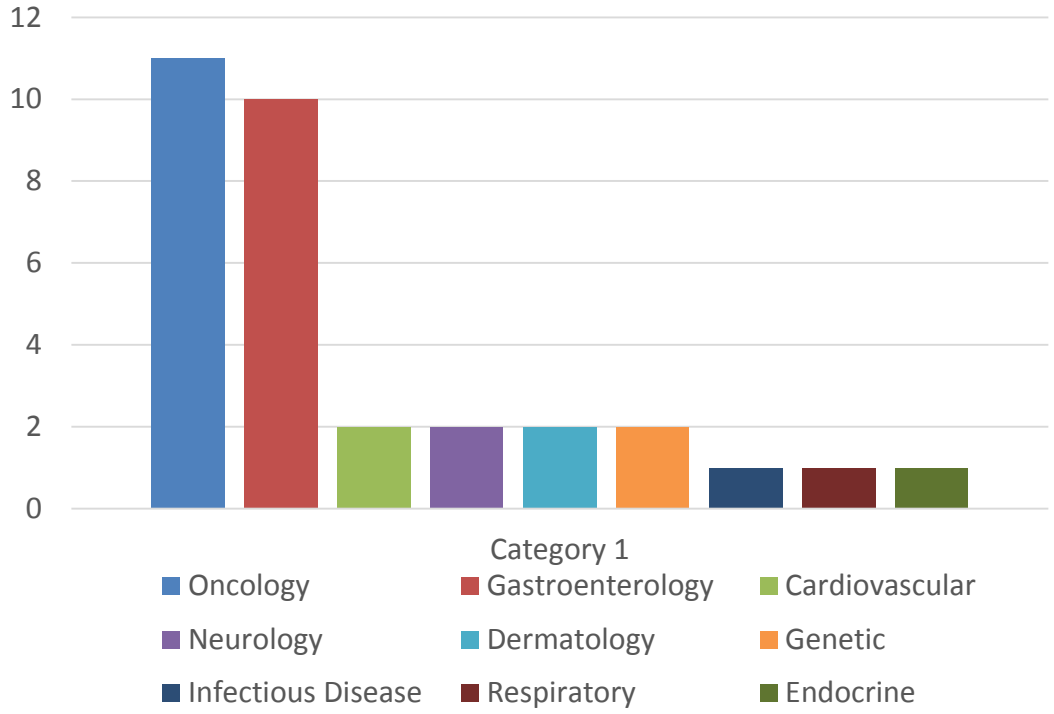
- Rapid pace of technology and exponential complexity demand both
  - Open, non judgemental scientific discourse
- Society holds us accountable
  - Increased transparency of regulatory decisions
- FDA and EMA have many connections and collaborations
  - Ad hoc topic discussions
  - Workshop participation at home and professional meetings
  - Formal engagements called, “clusters”
- Mutual goal is to ensure connectivity in critical areas
  - Many activities include other regions, such as Japan and Canada

The Pediatric Cluster

- Established in August 2007
- At least monthly informal discussions among regulators, which currently includes FDA, EMA, Health Canada, Japan's PMDA and Australia's TGA
- August 2007 – February 2018
  - 125 teleconferences with discussion of 473 product specific issues and 156 general topics (e.g. safety concerns related to a product class)
- CY 2017
  - 73% convergence on the issues
  - Frequently discussed product issues: scope of pediatric product development, safety, trial design, endpoints and study population

The Pediatric Cluster – Common Commentary

- Tool to inform sponsors of products discussed at the Pediatric Cluster
- Discussion points, identifying similarities and/or differences in FDA's and EMA's approach, are summarized and approved by FDA and EMA
- Approved 1-2 page common commentary document sent to sponsor
  - Comments sent are NOT binding on either Agency (i.e. they do NOT constitute regulatory advice).



Workshops and Working Groups

- Working Groups
  - Inflammatory Bowel Disease WG for ulcerative colitis: Jan-Dec 2012
  - Inflammatory Bowel Disease WG for Crohn's Disease: Jan 2014-June 2015
- Workshops
  - Gaucher Disease : September 2012
  - EMA FDA HC Pediatric Pulmonary Arterial Hypertension :June 2017
  - Advancing the Development of Pediatric Therapeutics (ADEPT)
    - ADEPT 1: Pediatric Bone Health, June 2014
    - ADEPT 2: Evaluation of Long-term Neurocognitive Development in Pediatrics, April 2015
    - ADEPT 3: Successes and Challenges of Performing Long-term Pediatric Safety Studies, April 2016
    - ADEPT 4: on Big Data,September 2017
  - CERSI University of Maryland - Pediatric Heart Failure, October 2017

Other Examples of Collaboration

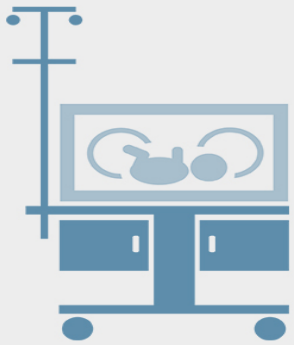
- International Council on Harmonization
  - Guideline development
    - Clinical Investigation of Medicinal Products in the Pediatric Population (2017)
    - Pediatric extrapolation - work on-going
- FDA-EMA Visiting staff fellowships
- Expert Meetings – regulator sponsored
  - Diabetes; HIV; rheumatology; extrapolation; osteoporosis

International Neonatal Consortium

INC AND THE NICU

The International Neonatal Consortium will concentrate its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of pre-term birth.

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

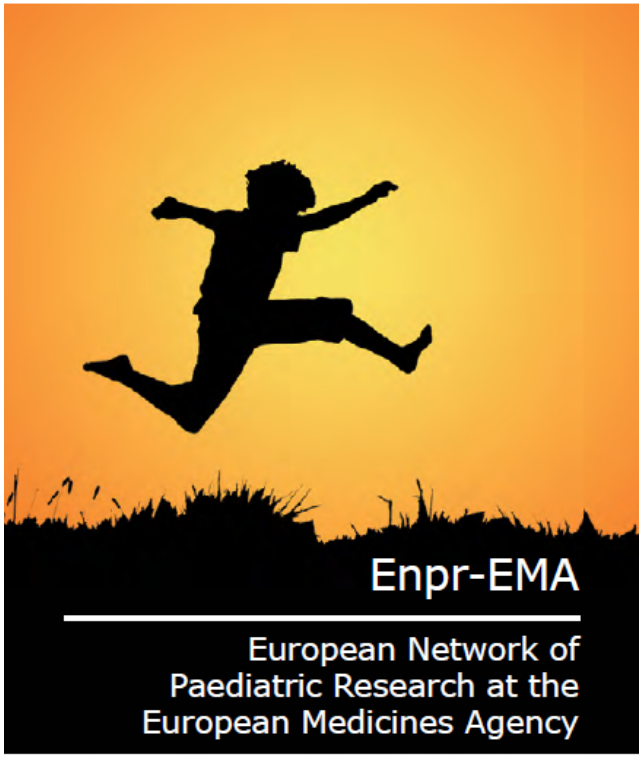


- NEONATAL LUNG INJURY AND CIRCULATORY FAILURE
- PERINATAL/NEONATAL INFECTIONS
- NEONATAL ABSTINENCE SYNDROME (NAS)
- RETINOPATHY OF PREMATURITY (ROP)
- NEONATAL GASTROINTESTINAL INJURY
- NEONATAL BRAIN INJURY
- DRUGS TO PREVENT PRETERM LABOR

Trial Networks

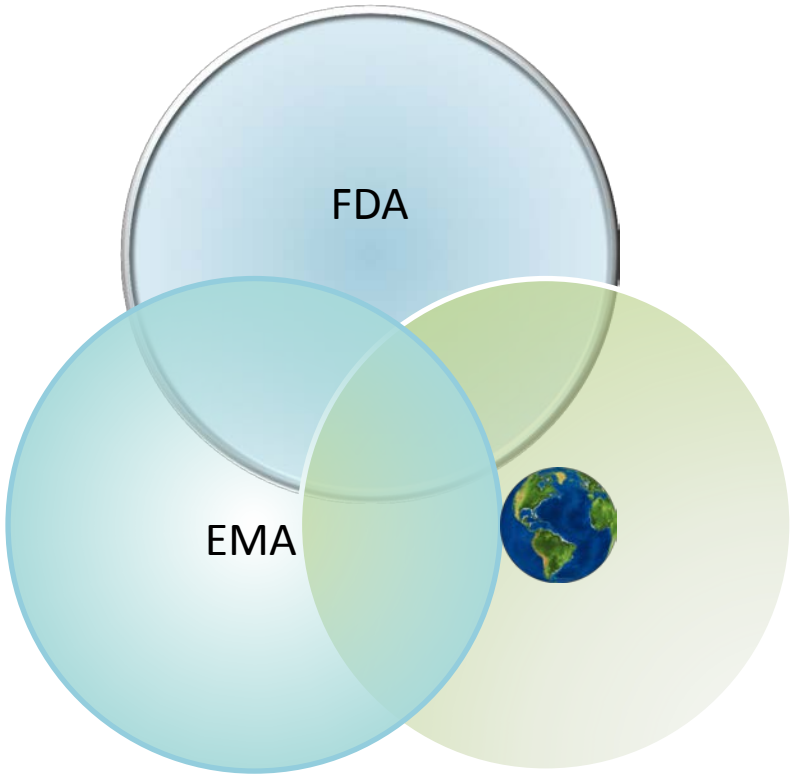
Enpr-EMA
European Network of Paediatric Research at the European Medicines Agency

I-A-C-T INSTITUTE FOR ADVANCED CLINICAL TRIALS FOR CHILDREN



What influences our collaboration?

- Legislation
  - Affected agency must reframe approach and apply to development programs
  - FDA requirements for pediatric development plus EMA's PIP require a lot of shifting of discussions in the Pediatric Cluster
- Societal shifts force regulators to confront change and adapt - together



What have we learned through the Cluster?

True collaboration is hard work

- Beware process and procedures that lock in rigidity
- Collaboration must be resourced
- Have the courage to change
  - FDA-EMA agreed 2016 to seek alignment on pediatric development programs for all products
  - Willingness to reassess need and direction
  - “What is needed” can change overnight
- Open minds to new science and changing course is essential

RACE for Children Act 2017

*Title V of the **FDA Reauthorization Act (FDARA),** August 18, 2017*

- **Requires** evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer."
  - Drug A treats lung cancer in adults, by attacking "molecular target ZFG"
  - No equivalent lung cancer in pediatrics
  - Pediatric cancer has "molecular target ZFG" at its root
  - RACE allows FDA to require studies of the pediatric cancer with Drug A
- **Molecularly targeted pediatric cancer investigation**: clinically meaningful study data, "using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling." [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Activities for FDA

- Establish list* of "**relevant targets**" to be updated regularly (1 year)
  - Molecular mechanisms that are known or expected to be relevant in pediatric cancer
- Establish list* of **non-relevant targets** (1 year)
  - This will allow for waivers for pediatric studies
- Seek broad input
  - Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates
  - Includes hosting an open public meeting to refine/generate lists of molecular targets of relevance in pediatric cancer (1 year)
- Be clear, communicative and transparent
  - Issue guidance on implementation (2 years)

**With National Cancer Institute (NCI)*

Implications for FDA

- "Broad input" is a lot of work.
  - Many stakeholders with a lot to contribute
  - NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates on many aspects
- Implementing will predate final guidelines
  - We have to start advising companies now – they must develop initial pediatric study plans (iPSP)for marketing applications expected to be submitted after August 2018

April 2018
Open Public Hearing on lists

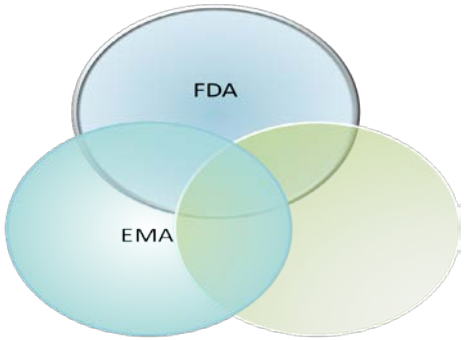
June 2018
Pediatric Oncology Advisory Committee meeting

Successful Implementation of RACE

- Be ready for potentially adverse consequences
  - Not a risk free endeavor
  - Transparency with all stakeholders
- Expand pediatric pre-clinical testing initiatives
  - Effective Industry-Academic collaboration
- Recognize and anticipate scientific discovery
- International collaboration will be important

International Collaboration and Coordination

- Work with industry and regulatory partners to avoid duplication and delays
- A big challenge as pace of RACE is rapid
  - US and EU requirements/processes/timelines sometimes collide
- Experience in Pediatric Cluster will be essential but will also need to bring in broader perspectives from oncology
  - Will require deft management



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It is up to regulatory bodies to show leadership in bringing both to sound development of pediatric medicines, and no one agency can go it alone.