Global collaboration:
between regulatory agencies
with paediatric research networks

Annual Enpr-EMA workshop
16 May 2017

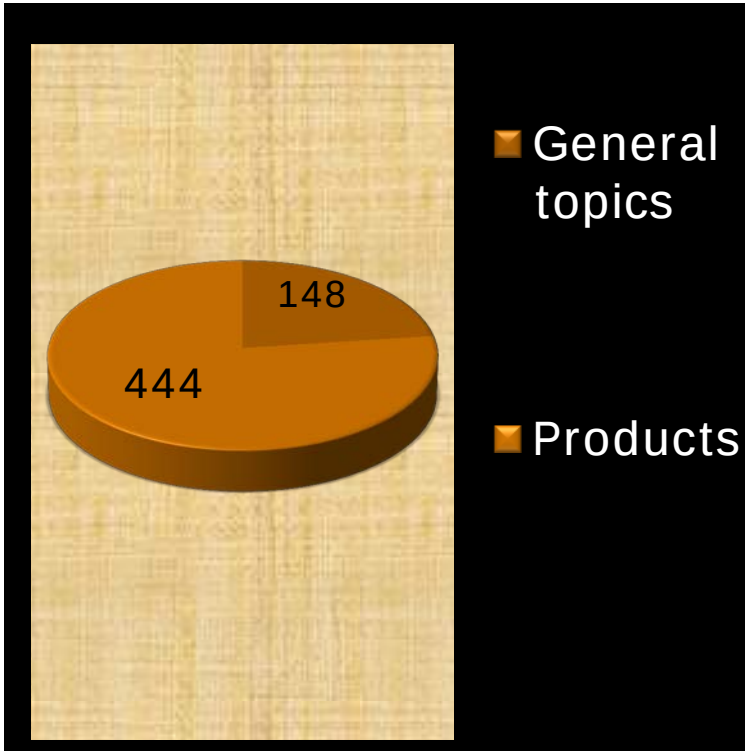
Presented by Irmgard Eichler
Senior Scientific Officer
Paediatric Medicines Office, EMA
Co-Chair Enpr-EMA

and

Susan McCune
Director, Office of Pediatric Therapeutics
Office of the Commissioner, FDA

How do regulators address global development in paediatric medicines?

Topics discussed 08/2007- 03/2017
Paediatric Cluster N=592



- We talk to each other frequently
- EMA/FDA **Paediatric Cluster** together with Health Canada, PMDA (Japan), and TGA (Australia)
- Monthly 2-3 hour teleconferences to discuss products/general issues
- More than one approach may be possible, but unnecessary studies are to be avoided
- Understand rationale when scientific approaches differ
- Aim for harmonization to the extent possible

Pediatric Cluster

- Frequently discussed product issues include scope of pediatric product development, safety, trial design and endpoints
- Convergence on approaches have been achieved for 73% of the issues discussed in the past 3 years
- In the US, since 1997, over 650 products have been labeled with additional information gathered from pediatric trials.
- In the EU since the implementation of the Regulation, from 2007 until 2015, 238 new medicines for use in children and 39 new pharmaceutical forms appropriate for children were authorised.

Experience with paediatric cluster

FDA

EUROPEAN MEDICINES AGENCY

Topics discussed at paediatric cluster T-conferences

Product specific discussions:

Waiver
Quality, Non-clinical
Paediatric overall development
Adult study results - Paediatric study results
Indication
Population , Age groups
Study design, Sample size
Dose, Endpoints
Safety
Extrapolation
Timelines
Long-term follow-up

General discussions:

Endpoints

Extrapolation

Meetings/workshops

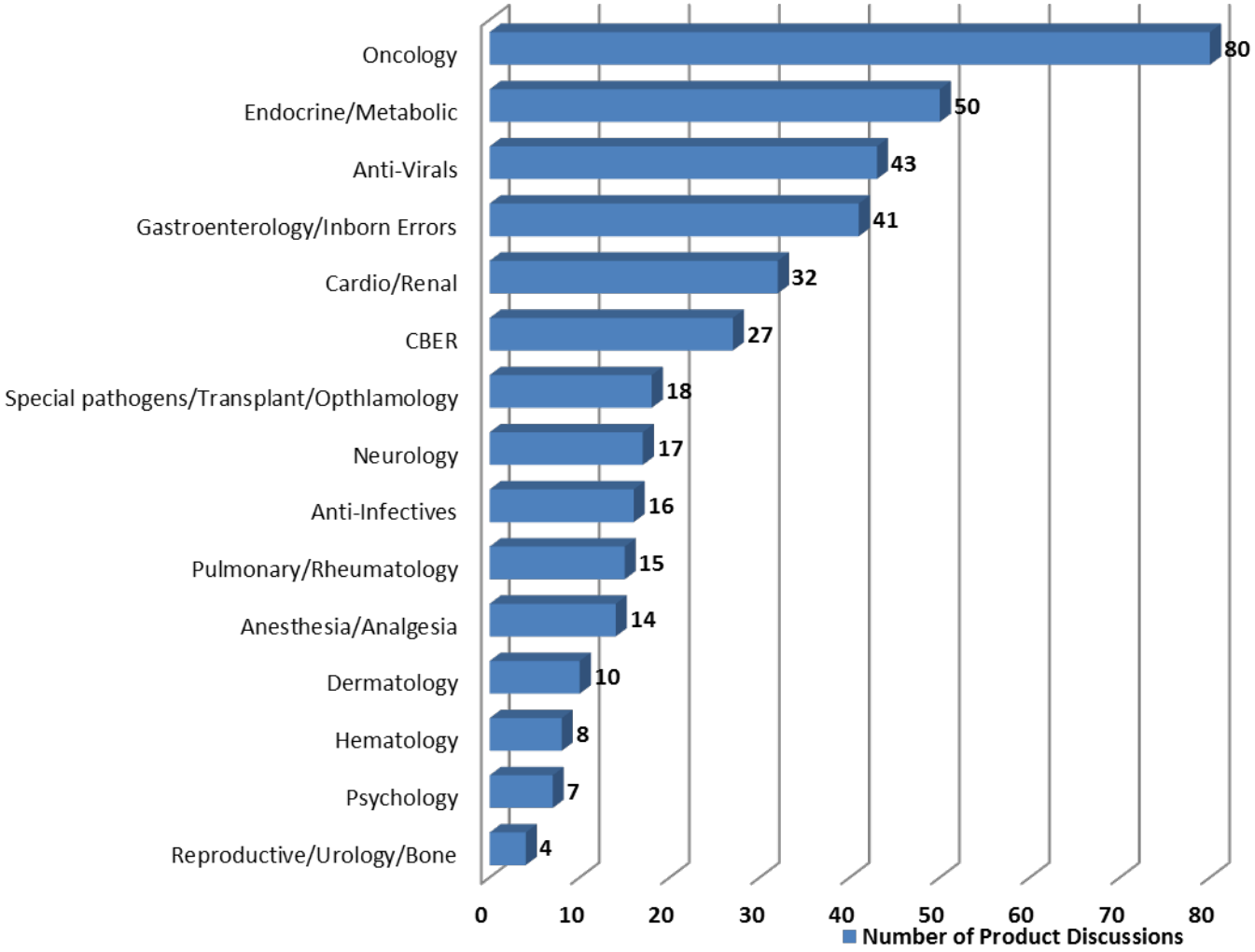
Joint publications

Regulatory action

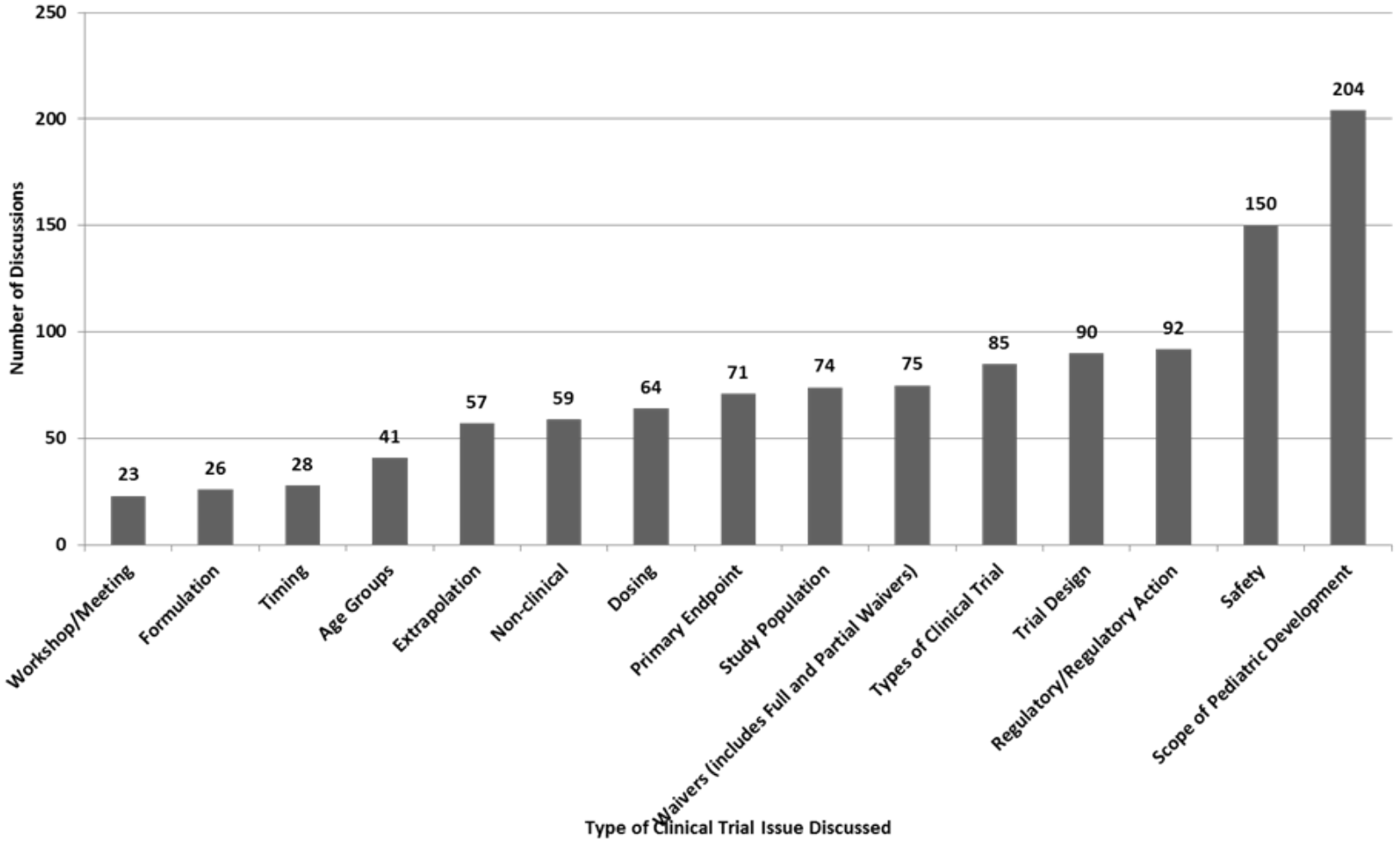
Pediatric Issues to the Pediatric Cluster

- Individual divisions have varying levels of pediatric expertise and international experience
- The Pediatric Cluster avoids fragmentation of pediatric development activities
- The Pediatric Cluster is responsible for ensuring the appropriate pediatric and other subject matter experts are in attendance
- The Pediatric Cluster provides additional coordination with PeRC and other divisions

Pediatric Cluster Products Discussed by Division 2007-2015
n=382



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



Common Commentary Issues 2012-2017 (N= 25)

- Oncology n=10
- Gastroenterology n= 9
- Cardiology n=2
- Neurology n= 1
- Dermatology n=1
- Inborn Errors n=1
- Antimicrobial n=1

Pediatric Cluster: Resolving Differences Example: Patient Population

- Oncology product to treat a specific type of medulloblastoma

- Proposed by sponsor
  - To EMA: newly diagnosed and relapsed/refractory patients
  - To FDA: relapsed/refractory patients only

- Discussion outcome:
  - FDA requested the sponsor to study both patient populations

Pediatric Cluster: Resolving Differences Example: Timing of Pediatric Studies

- Drug "X" as add-on to insulin to treat T1DM

- Positions prior to discussion
  - EMA: after efficacy and safety data are available in adults with T1DM as this add-on drug is the first in its class to be studied in children with T1DM.
  - FDA: sufficient to have interim adult T1DM data and pediatric PK/PD T2DM data in patients who received this product since there is a significant unmet need (many children and adolescents with T1DM do not achieve their glycemic targets on insulin alone)

- Discussion outcome
  - EMA understood FDA's rationale and aligned with FDA on earlier timing to address the significant unmet need

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**

Joint Pediatric Working Groups, Workshops and Expert Meetings

- **Working Groups**
  - Inflammatory Bowel Disease WG for ulcerative colitis: Jan-Dec 2012
  - Inflammatory Bowel Disease WG for Crohn's Disease: Jan 2014-June 2015
  - Pediatric Rare Disease WG: new WG to be established as a permanent WG of the Pediatric Cluster
- **Workshops**
  - Gaucher Disease Workshop: September 17-18, 2012
  - Pediatric Pulmonary Hypertension: June 2017
  - Advancing the Development of Pediatric Therapeutics (ADEPT)
    - ADEPT 1: Pediatric Bone Health on June 3, 2014
    - ADEPT 2: Evaluation of Long-term Neurocognitive Development in Pediatrics April 17, 2015
    - ADEPT 3: Successes and Challenges of Performing Long-term Pediatric Safety Studies April 13-14, 2016
    - ADEPT 4: on Big Data- planned for September 18-19, 2017
- **Expert meetings**
  - e.g. diabetes, HIV, rheumatology and osteoporosis
- **Additional pediatric WGs and Workshops will be established on an ad hoc basis whenever extended in-depth discussions are needed and they will be an extension of the Pediatric Cluster**

IMPACT OF THE FOOD AND DRUG ADMINISTRATION (FDA)- EUROPEAN MEDICINES AGENCY (EMA) COMMON COMMENTARY ON PEDIATRIC CANCER DRUG 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. Mali, and D Murphy

Office of Hematology and Oncology , CDER and Office of Pediatric Therapeutics, OC, U.S. FDA and the Paediatric Committee, EMA

BACKGROUND

- The U.S. and the EU have specific laws which direct their respective regulatory agencies, the FDA and the EMA, in the development and the evaluation and licensing (market authorization) of drugs for children.
- These laws are the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) in the U.S. and the Paediatric Regulation (EC) No. 1901/2006 in the EU.
- Despite similar objectives, differences exist in the requirements and the timing of submission of plans for pediatric evaluation of new drugs which reportedly could result in delayed access to new agents for early phase evaluation.
- Assuring that plans for evaluation of new drugs in the U.S. and EU are at least complimentary and neither duplicative nor competing has the potential to expedite/facilitate the study of relevant candidate therapies for childhood cancer.
- The FDA and the EMA have a comprehensive confidentiality agreement which permits scientific exchange in an effort to provide consistent regulatory advice for global development programs when possible. In addition, the agencies provide
  - **Parallel Scientific Advice (PSA)** - formal regulatory process
  - **Common Commentary (CC)** - nonbinding scientific advice generated from monthly international regulatory agency teleconferences (Pediatric Cluster Calls)
- Providing a sponsor with an integrated regulatory recommendation reflecting the scientific discussion(s) between FDA and EMA on the proposed development plan of a specific agent is often beneficial.
- The CC process is undertaken by the Agencies on their own initiative; sponsors can also request an integrated scientific assessment of a proposed new drug development plan .

OBJECTIVES

- To review the Pediatric Cluster Call experience to determine the frequency with which CCs were considered to accelerate pediatric development plans
- To assess the impact of the CC on the subsequent pediatric studies of a given product.

(Poster accepted for the 48th Congress of the International Society of Paediatric Oncology October 19-22, 2016 in Dublin, Ireland)

METHODS

- Retrospective review of the Pediatric Cluster Calls from the Office of Pediatric Therapeutics from 10/2012 to 3/2016 to assess prevalence of oncology product discussion and resulting Common Commentaries.

RESULTS

- Focus of discussions frequently pertained to toxicity; non-clinical data vs. adult patient experience and suggested monitoring plans, eligible patient populations and planned indication (s) and study design (Table 1).
- During the 36 month period evaluated, 46 scientific discussions of 26 distinct oncology products occurred. CCs were created for 8 products (Table 2).
- Additional discussions were held on a proposed master protocol platform under review by both agencies.
- Global collaborative studies were recommended in many cases.
- All Common Commentaries directly influenced decisions on Paediatric Investigation Plans (PIPs), Pediatric Study Plans (PSPs), and Written Requests (WRs).
- The initial CC resulted in formal PSA in some cases.
- All sponsors have expressed appreciation for the CC.

TABLE 1: PEDIATRIC CLUSTER CALL DISCUSSIONS

SCIENTIFIC FOCUS AREAS	#
Relevance of the product for pediatric development-addressing a meaningful unmet clinical need and potential benefit	26
Toxicity concerns, either non-clinical or early adult data	18
Appropriate monitoring plans based on toxicity data	18
Supporting data for starting dose and planned escalation	15
Feasibility and emerging results from potentially competing studies	12
Eligible patient populations	6
Study endpoints	3
Other pharmacology issues	3

TABLE 2: EXAMPLES OF FDA EMA COMMON COMMENTARIES 2012-2016

PRODUCT	SPONSOR	DATE	DISCUSSION TOPICS
Sonidegib	Novartis	2012	Toxicity, eligibility, indication, in vitro diagnostic assay, unmet clinical need.
Volasertib	Boehringer Ingelheim	2013	Eligibility, indication, trial design, unmet clinical need
Nivolumab	BMS	2013	Toxicity, eligibility (age-related concerns), indication, dosing plans, combination therapy plans, trial design, potential for partial extrapolation
Blinatumomab	Amgen	2013	Toxicity, eligibility, indication, trial design, dosing optimization
Evofosfamide	Threshold	2013	Relevance to pediatric cancer, clinical pharmacology, trial design, potential for partial extrapolation
Inotuzumab	Pfizer	Not sent	Toxicity, eligibility, indication, trial design
Oncology Matrix Proposal	Roche/ Genentech	2015	Eligibility, indication, trial design
Dabrafenib	Novartis	2016	Toxicity, eligibility (age-related concerns), indication, dosing plans, combination therapy plans, trial design, in vitro diagnostic assay

- Cancer drug development is a global enterprise; the required collaboration for the investigation of new agents is expected to increase as smaller subpopulations of children with low incidence cancers are identified as candidates for evaluation of new targeted drugs. With limited numbers for evaluating targeted drugs in enriched populations, duplication and competing studies must be avoided.
- The Agencies systematically collaborate, using all of their experience with innovative drugs, to support paediatric assessments of products.
- Coordinated international scientific review and discussion of initial development plans can result in early (when appropriate) and efficient evaluation of new agents.

Proactively Addressing Study Feasibility Including Better Interactions With Academia

EU - US strategic meeting on the future of paediatric medicine 09/2016

- Representatives from the EC, EMA, FDA
- Discussion focused on how to harmonize and further streamline global paediatric product development
- Envisioned goal for the next few years: Aim for a convergent and harmonised paediatric development programme for each medicine

through

- Early proactive collaboration
- Joint outreach programmes to identify high priority needs and to facilitate related research and development
- Collaboration with all stakeholders to bring experts, researchers and industry together
- Organisation of joint initiatives to bring stakeholders together
- Paediatric Cluster to serve as key forum for continued discussion and resolution of scientific issues among regulators

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/12/WC500218004.pdf

EU - US strategic meeting on future of paediatric medicine

- **Joint outreach programmes to identify high priority needs and to facilitate related research and development**
- **Collaboration with all stakeholders to bring experts, researchers and industry together**
- **Organisation of joint initiatives to bring stakeholders together**

What has been done in the meantime ?

- First EMA-FDA-Health Canada jointly organised workshop on paediatric pulmonary hypertension (June 2017)
- Enpr-EMA working groups with participation of networks, industry and PDCO members
- Regular face to face meetings between research networks and PDCO during PDCO plenary
- Multistakeholder paediatric oncology workshop
- Principles on the involvement of young patients within EMA activities
- European network of young people advisory groups – member of Enpr-EMA

Proactively Addressing Study Feasibility Including Better Interactions With Academia

- Pediatric master protocols
- Pediatric trial networks
- Pediatric consortia
- Pediatric registries
- Opportunities for education
  - FDA's Clinical Investigators Training Workshop every 2 years
    - Directed to academic investigators
    - Next workshop in Fall, 2018

International Neonatal Consortium (INC)

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**

BC Children's Hospital
Boston's Children Hospital
Brighton and Sussex Medical School
Canadian Neonatal Network/University of Toronto
Children's Hospital at Montefiore
Children's Hospital of Philadelphia
Children's Mercy Hospital, Kansas City
Children's National Medical Center
Cincinnati Children's Hospital Medical Center
City University, London
Columbia University Medical Center
Cordelier Research Center, French National Institute of Health and Medical Research, Inserm
Diderot University, Paris
Duke University
Great Ormond Street Hospital
Harvard University
Hospital for Sick Children, Toronto, Canada
Imperial College London
Riley Hospital for Children, Indiana University Health
Jackson Memorial Medical Center, Miami
Johns Hopkins University
Karolinska University Hospital
King's College, London
National Center for Child Health and Development, Tokyo
Mount Sinai Hospital
Nagano Children's Hospital
Nagoya University Hospital
Northern Clinical School, Sydney, Australia
NorthShore University Health System
Osaka Medical Center and Research Institute for Maternal and Child Health
Oxford University
Queen Mary University of London
Rīga Stradiņš University Hospital, Latvia
Robert Debré University Hospital, Paris
S. Paris U. Hospitals
Saint-Pierre University Hospital
Samsung Medical Center, Seoul, South Korea
Showa University
Erasmus MC-Sophia Children's Hospital, Netherlands
Southern Illinois University School of Medicine
St. Marianna University
Stanford University
Thomas Jefferson University
Tokyo Women's Medical University
Tufts Medical Center
Uniformed Services, University of the Health Sciences
University Hospital Agostino Gemelli, Rome
University Medical Center Utrecht
University of Liverpool
University College Cork
University College London Hospital
University Hospital of Brooklyn
University Medical Center Freiburg
University of California, Davis
University of California, San Diego
University of California, San Francisco
University of Colorado
University of Florida
University of Gothenburg, Sweden
University of Leuven
University of Liverpool
University of Lübeck
University of Maryland
University of Michigan
University of Montreal
University of North Carolina at Chapel Hill
University of Otago Christchurch
University of Siena, Italy
University of Tartu, Estonia
University of Ulm
University of Utah
University of Washington
University of Wurzburg, Germany
University of Zurich
Vereniging van Ouders van Couveusekinderen (VOC)
Vermont Oxford Network
Yonsei University College of Medicine

Academic Partners

N=77

International Neonatal Consortium (INC)

Regulatory Partners

Australia and New Zealand Neonatal Network
European Medicines Agency
Health Canada
Korean Neonatal Network
National Institutes of Health
National Security Agency of Medicines and Health Products, France (ANSM)
Norwegian Medicines Agency
The Pediatric Network in Canada
Pharmaceuticals and Medical Devices Agency, Japan (PMDA)
U.S. Food and Drug Administration

N=10

Parent and Patient Advocacy Partners

BLISS
Council of International Neonatal Nurses (COINN)
Graham's Foundation
March of Dimes
National Association of Neonatal Nurses (NANN)
NEC Society
Preemie Parent Alliance

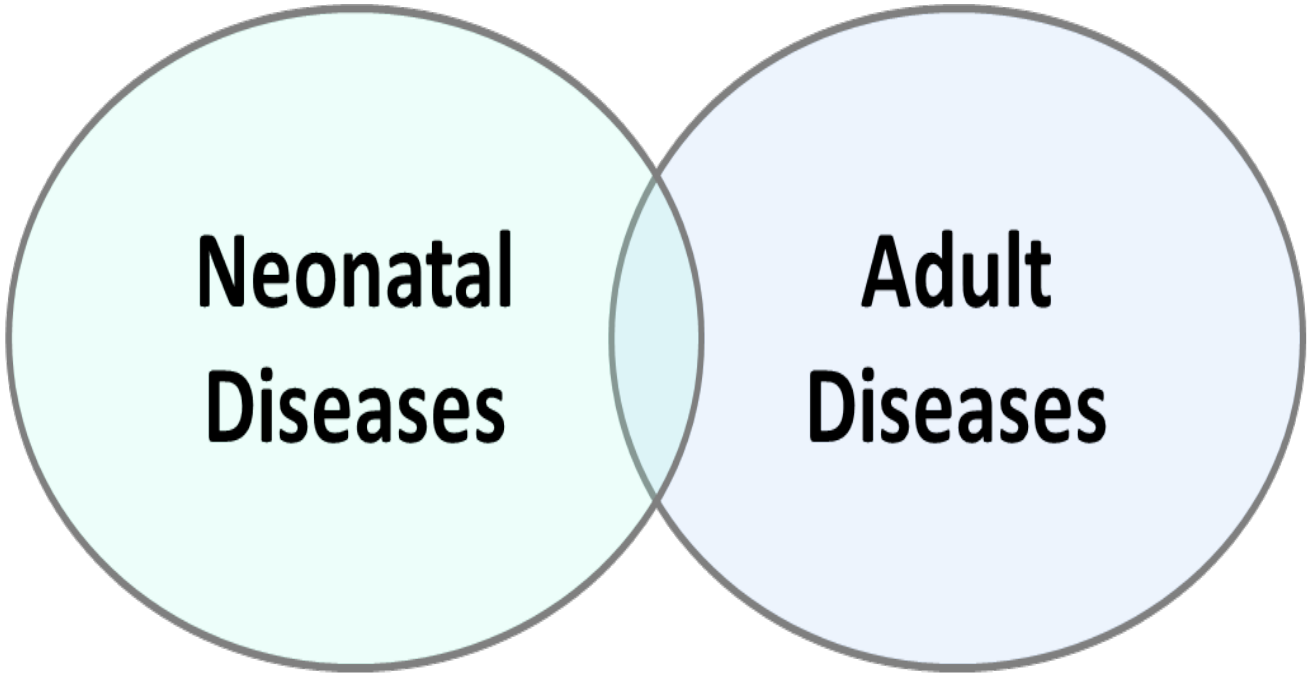
N=7

Industry Partners

Chiesi Pharmaceuticals
Eli Lilly and Company
Janssen Research & Development
Novartis Pharmaceuticals
Parabase Genomics
Pfizer Inc
Sanofi Pharmaceuticals
Shire

N=8

Drug Development Disconnect



Majority of drugs used are off-label

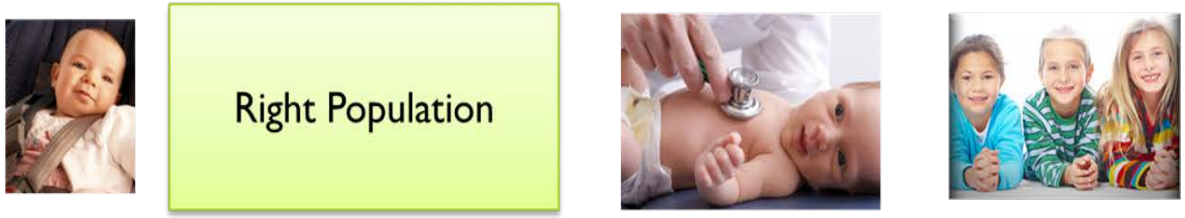
Pediatric Plans to include neonates

Very few new therapies are being developed specifically for neonates

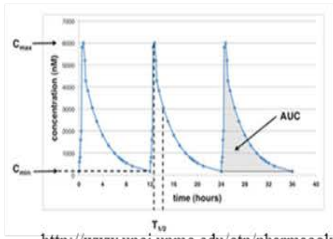
Drug Development Paradigm

Right Drug

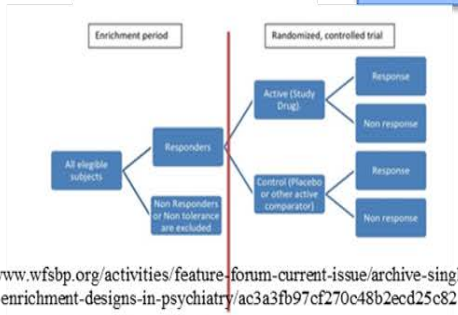
Right Population



Right Dose

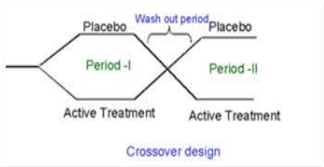


http://www.upci.upmc.edu/ctp/pharmacokinetics.cfm

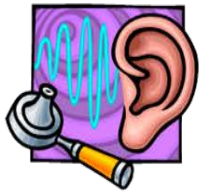


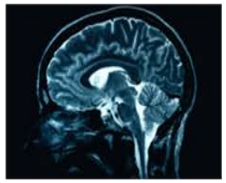
http://www.wfsbp.org/activities/feature-forum-current-issue/archive-single/should-we-accept-enrichment-designs-in-psychiatry/ac3a3fb97cf270c48b2ecd25c825ee9b.html

Right Trial Design

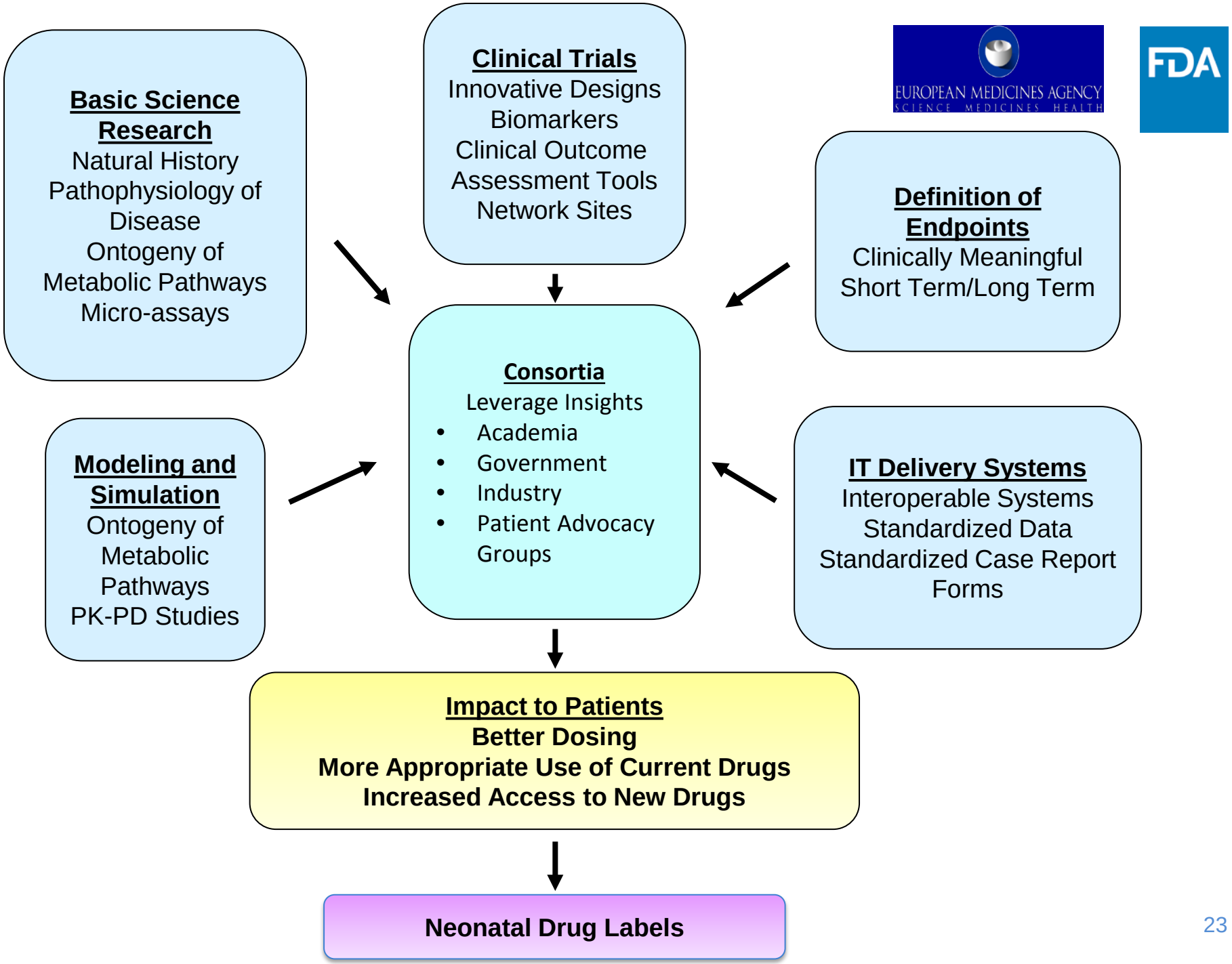


http://accp1.org/pharmacometrics/theory.htm

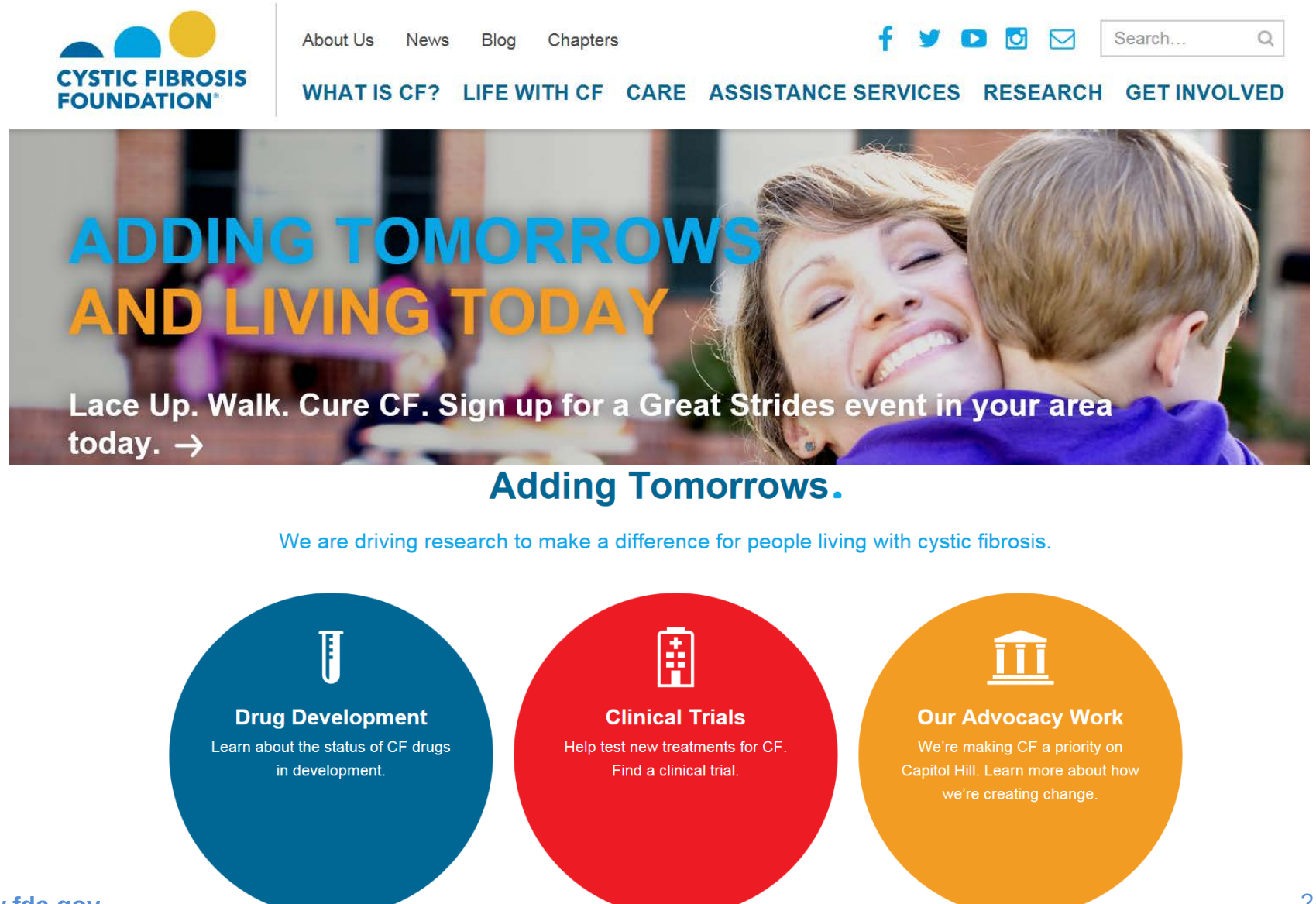




Right Endpoints


Basic Science Research
Natural History
Pathophysiology of Disease
Ontogeny of Metabolic Pathways
Micro-assays
Clinical Trials
Innovative Designs
Biomarkers
Clinical Outcome Assessment Tools
Network Sites
Definition of Endpoints
Clinically Meaningful
Short Term/Long Term
Consortia
Leverage Insights
Academia
Government
Industry
Patient Advocacy Groups
Modeling and Simulation
Ontogeny of Metabolic Pathways
PK-PD Studies
IT Delivery Systems
Interoperable Systems
Standardized Data
Standardized Case Report Forms
Impact to Patients
Better Dosing
More Appropriate Use of Current Drugs
Increased Access to New Drugs
Neonatal Drug Labels

Patient/Parent Advocacy Groups



https://www.cff.org/

Conclusion

- Ongoing harmonization of paediatric science/research to make paediatric product development easier and faster
- Collaboration with all stakeholders essential
- Joint outreach initiatives to bring stakeholders together

Plans / suggestions for the future:

- Education:
  - Training in regulatory science and procedures for members of networks
  - Disease-specific training sessions for regulators
- Collaboration, including young people, in guideline development and in development of paediatric inventories on therapeutic needs
- Creating of networks' contact points to facilitate experts' identification and procedural participation within strict timelines
- Global collaboration between regulatory agencies and international networks:
  - Institute for Advanced Clinical Trials for Children
  - IMI2 – Pan European Paediatric Research Network

Acknowledgments

- Thanks to Dr. Jean Temeck for Coordinating the Pediatric Cluster for the FDA and Sharing Slides for this Presentation
- Thanks to Aline Labejof for Coordinating the Paediatric Cluster for EMA


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Back-up slides

Pediatric Cluster: Resolving Differences Example: Endpoints

- 2 recombinant human products to treat rare genetic metabolic diseases

- Positions prior to discussion
  - EMA: sponsor's proposed surrogate acceptable as primary endpoint
  - FDA: clinically meaningful endpoints needed to assess efficacy

- Discussion Outcome
  - FDA and EMA agreed on approach
    - Need to include clinically meaningful endpoints
    - The totality of the evidence will be considered in the assessment and clinical benefit must be demonstrated

Managing Life Cycle After Approval of PIP and PSP

- Co-ordinate pediatric product development with adult development (already being addressed with the legislation)
- Enroll pediatric patients in studies BEFORE approval of product in adults to decrease off-label use
- Regulatory agency authority to modify an agreed PIP or PSP, as needed, based on feasibility or evolving science/data

Role for academia – networks for drug approval

- Standardised clinical trial training
- Standard of care
- Response to treatment: Standardised core outcome measures
- What are acceptable control groups?
- Long-term outcomes (especially for remission/safety)
- Use of registries