Best Pharmaceuticals for Children Act (BPCA) Framework to Enable Pediatric Drug Development

Resources Lists

February 2022
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Introduction

The National Institutes of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) Program (https://www.nichd.nih.gov/research/supported/bpca/history) has, for the last 18 years, sponsored a pediatric drug development program of off patent medications used in children. The primary goals of the program include identifying existing needs in pediatric therapeutics, prioritizing those needs, sponsoring clinical studies to improve dosing, safety and effectiveness data in those prioritized areas, and submitting the clinical study data to the FDA for potential drug label updates that aim to improve the knowledge of medications used in children. The Program has been very successful in its mandate to improve knowledge gaps and has, to date, conducted over 40 clinical trials which include more than 200 molecules, provided data to the FDA in the form of clinical study reports for over 26 molecules, and achieved 17 label changes.

In early 2020, the Program conducted an analysis of the metrics and outcomes of the clinical program, including prioritization goals, study outcomes, and remaining gaps in pediatric therapeutics. As part of that analysis, the Program reviewed historical data from past prioritizations and previous BPCA working groups to determine remaining and unaddressed therapeutic gaps in knowledge (2008-2018). Many topics of interests and unanswered questions arose from this review, but one recurring theme stood out as a potential actionable item:

Is it possible to develop a **generic framework** that:

• can be useful to and utilized by various stakeholder involved in pediatric drug development/research, and that

• can subsequently be customized to specific therapeutic areas, indications, type of drug, developmental stages, and phenotypic expression?

As a part of the initiation of this call for a generic framework of resources, the NIH BPCA Program held its annual Stakeholders Meeting on December 14-15, 2020 and discussed this concept with our stakeholders. At that meeting, the NIH staff and the Pediatric Trials Network (https://pediatrictrials.org/) investigators provided updates on the current progress within the clinical program and then held breakout sessions focused on drug development issues identified as part of the BPCA analysis as remaining scientific gaps in pediatric drug development. Meeting minutes can be found here: https://www.nichd.nih.gov/sites/default/files/inline-files/BPCA12-15-2020StakeholdMeetSum.pdf.

Since the meeting in December 2020, development of the BPCA Framework to Enable Pediatric Drug Development, spearheaded by the NICHD BPCA Program, has made steady progress throughout 2021. Subject matter experts in pediatric care collaborated to research, identify, submit and review available resources of scientific articles, book chapters, and reports. The framework will give stakeholders involved in pediatric therapeutics research, including new and junior investigators applying for grants, access to a multitude of resources to review prior to writing grant proposals and/or before conducting pediatric drug development research. The goal is to have an annotated, selected, and curated collection of resources that will indicate which resources are essential, “read this first,” and when other resources will be useful. Resources of universal interest will be identified along with resources that relate to specific topics in pediatric drug development and to specific clinical populations.
Resource Focus Areas

- General Pediatric Drug Development Resources and Guidances
- Advancing Clinical Trial Designs and Conduct in Pediatric Drug Development
- Emphasizing Pharmacodynamic Biomarkers in Pediatric Drug Development
- Enhancing Research in Pediatric-Friendly Formulations
- The Relevance of Pharmacoepidemiology in Informing Pediatric Drug Development
- How Pharmacokinetic Modeling Can Be Used to Inform Drug Dosing
- The Role of Quantitative Systems Pharmacology in Pediatric Drug Development

Resource Classifications

- Read This First
  Essential overview documents
- Helpful Explanation
  Resources that offer further explanation
- Additional Resources
  Resources for specific situations or are not public
- U.S. Guidances
  Relevant FDA guidance documents

Stakeholder Impact

Pediatric drug development encompasses a vast variety of stakeholders engaged in expanding research knowledge, as well as improving outcomes, access and public health impact. These various stakeholders could certainly benefit from increased efficiency of access to documents as well as the possibility of increased likelihood of useful contributions to each other’s work. The table below describes benefits to stakeholders involved with the framework.

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<th>Stakeholders</th>
<th>Benefits</th>
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<td>Clinical Investigators</td>
<td>Greater understanding of the impact of drug labelling and increasing knowledge of study design and conduct choices</td>
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<td>Preclinical Investigators</td>
<td>Identifying potential mechanisms for targeted contributions to clinical work so that can be applied optimally</td>
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<td>Regulators</td>
<td>Greater awareness of the expanse of resources available to and utilized by researchers</td>
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<tr>
<td>Patients and their advocates</td>
<td>Increased awareness of the science behind clinical research and the importance of improving drug labeling</td>
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<td>Organizations (industry and others) that own assets for pediatric drug development (drugs, biomarkers, pre-clinical models, etc.)</td>
<td>Improved clarity about pathways to regulatory approval and more informed contributions from investigators</td>
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<td>Institutions (industry and others) that drive drug development (Sponsors) and Institutions (industry and others) that support drug development (e.g., Contract Research Organizations or Academic Research Organizations)</td>
<td>More informed contributions from investigators as a result of access to relevant guidance</td>
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**Program Leaders**

**Perdita Taylor-Zapata, M.D.,** is a Physician with the Obstetric and Pediatric Pharmacology and Therapeutics Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), where she leads the effort for the implementation of the Best Pharmaceuticals for Children Act (BPCA) at the NICHD. She is a pediatrician from the Washington Metropolitan area. She graduated from Howard University Medical School in 1994, and completed her pediatric residency training at the Children’s National Medical Center in Washington, D.C. After her residency, she worked at the National Institutes of Health Clinical Center as a clinic physician in the Pediatric HIV Working Group of the National Cancer Institute. There she spent 7 years taking care of the outpatient and inpatient medical needs of the HIV-positive pediatric patients enrolled in phase I/II clinical treatment trials. In addition to her role as a staff physician, she was also involved in medical research, writing parts of clinical protocols and conducting retrospective and prospective research projects. Since 2004, she has worked in OPPTB, starting as the primary outreach liaison for the BPCA Program, then as the Program official for the BPCA Data Coordinating Center (DCC), and now as the primary program lead for the entire BPCA Program, including the Pediatric Trials Network, the DCC and the logistics contract team. In addition to pediatric drug development, Dr. Taylor-Zapata also has research interests in pharmacoepidemiology, workforce diversity, and adverse effects of medications used in children.

**Mark Turner, Ph.D., MBChB,** is Professor of Neonatology and Research Delivery at the University of Liverpool, UK. He graduated from Manchester University with a medical degree in 1991 and a PhD in 1999 (placental physiology). He trained in neonatal medicine in the North West of England and has worked as a Consultant Neonatologist in Liverpool since 2005. His research aims to improve the access of newborn babies and children to high quality medicines. This has included studies of dosing, safety and efficacy, and research about excipients, manipulations of medicines, the avoidability of adverse drug reactions and the value of age-appropriate formulations. He believes that the coherent integration of the design and conduct of clinical trials is key to improving the quality of medicines. He works to develop efficient medicines research infrastructure in Europe and globally as Chair of the European Network for Paediatric Research at the European Medicines Agency (EnprEMA) (2013 – 2019), Convenor of the European Paediatric Clinical Trials Research Infrastructure, co-Director of the International Neonatal Consortium and as co-Coordinator of the Collaborative Network for European Clinical Trials for Children (conect4children, c4c).
General Resources in Pediatric Drug Development (PDD)

Read this First

1) E8(R1) General Considerations for Clinical Studies
   FDA. 2019.
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies

2) Guidance for Industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population
   FDA. 2000.
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11-clinical-investigation-medicinal-products-pediatric-population

3) General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
   FDA. 2014.

4) Clinical Trials in Children
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4345947/
Helpful Explanation

1) Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND
FDA. 2013.

2) Toolkit for Research and Development of Paediatric Antiretroviral Drugs and Formulations
https://www.who.int/publications/i/item/9789241514361

3) Reflection Paper on the Use of Extrapolation in the Development of Medicines for Pediatrics
EMA. 2018.

4) Frameworks for Evaluating Medicines in Children
https://www.clinicaltherapeutics.com/article/S0149-2918(17)30946-3/fulltext


6) Rare Pediatric Disease Priority Review Vouchers
FDA. 2019.

7) Safety, Dosing, and Pharmaceutical Quality for Studies That Evaluate Medicinal Products (Including Biological Products) in Neonates.
https://www.nature.com/articles/pr2016221

8) Pediatric Drug Development Regulatory Considerations
FDA. 2016.
https://www.fda.gov/media/100571/download
U.S. Guidances

1) Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry
   FDA. 2019.

2) Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
   FDA. 2020.

3) Exception from Informed Consent Requirements for Emergency Research
   FDA. 2013.
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research

4) Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices
   FDA. 2016.

5) COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders

7) Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans
   FDA. 2020.

8) General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry
   FDA. 2019.
Additional Resources


2) Informed Consent

3) Exploratory IND Studies

4) Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff

5) How to Comply with the Pediatric Research Equity Act

6) Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice

Advancing Clinical Trial Designs and Conduct in PDD

Read this First


Helpful Explanation

1) A Roadmap to Using Historical Controls in Clinical Trials—by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG)
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7069184/

2) Innovative Study Designs Optimizing Clinical Pharmacology Research in Infants and Children

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6751792/

4) Moving Forward in Clinical Research with Master Protocols
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8120789/

5) Informational Designs and Potential Applications to Rare Disease. In “Handbook of Biomarkers and Precision Medicine"
   https://u1lib.org/book/5410008/67f76d

6) FDA’s Clinical Investigator Course Preparing an IND Application: CBER Breakout Session; Putting Together Your IND Submission (CBER): Preclinical Considerations; Clinical Trial Design Expectations to Ensure Safety for a First-in-Human Clinical Investigation
   FDA. 2019.

7) Plan and Design with the Child in Mind: Global Pediatric Clinical Trials Network Recommendations and Insights for Sponsors of Pediatric Research

8) Best Practices for Adaptive Trials

9) European Regulators’ View on Platform Trials
   Paul-Ehrlich-Institut. 2018.
**Helpful Explanation - Specific Situations**

### Oncology

1) Clinical Pharmacology in the Adolescent Oncology Patient. 
[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018345/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018345/)

2) Joint Adolescent-Adult Early Phase Clinical Trials to Improve Access to New Drugs for Adolescents with Cancer: Proposals from the Multi-Stakeholder Platform-ACCELERATE. 
[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889024/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889024/)

3) Dose Titration Algorithm Tuning (DTAT) Should Supersede 'the' Maximum Tolerated Dose (MTD) in Oncology Dose-Finding Trials 
[https://f1000research.com/articles/6-112/v3](https://f1000research.com/articles/6-112/v3)

4) ACCELERATE Platform Links - Fostering Age Inclusive Research (FAIR) Trials 
[https://www.accelerate-platform.org/fair-trials/](https://www.accelerate-platform.org/fair-trials/)


### Cell and Gene Therapy

1) Expediting Clinical Development for Cell and Gene Therapies - Applying Master Protocol Concept in Early-Phase Trials 
[https://www.med.upenn.edu/cellicon2021/assets/user-content/documents/ke-liu-cellicon-valley-conference-may-6-2021-(1).pdf](https://www.med.upenn.edu/cellicon2021/assets/user-content/documents/ke-liu-cellicon-valley-conference-may-6-2021-(1).pdf)

2) Issues in Clinical Trial Design for Cell Therapy 
FDA. 2019.  
[https://pharm.ucsf.edu/sites/pharm.ucsf.edu/files/acdrs/media-browser/Issues%20in%20Clinical%20Trial%20Design%20for%20Cell%20Therapies.pdf](https://pharm.ucsf.edu/sites/pharm.ucsf.edu/files/acdrs/media-browser/Issues%20in%20Clinical%20Trial%20Design%20for%20Cell%20Therapies.pdf)
3) Adaptive Dose-Finding Based on Safety and Feasibility in Early-Phase Clinical Trials of Adoptive Cell Immunotherapy  
[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211137/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211137/)


**Infections**

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471052/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4471052/)

2) Meeting the Goal of Concurrent Adolescent and Adult Licensure of HIV Prevention and Treatment Strategies  
[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5685924/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5685924/)

3) The HIV Drug Optimization Agenda: Promoting Standards for Earlier Investigation and Approvals of Antiretroviral Drugs for Use in Adolescents Living with HIV  
[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7459170/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7459170/)

4) Model Informed Drug Development Approaches for Immunogenicity Assessments Workshop  
FDA. 2021.  

**Neonates**

1) Clinical Trials of Medicines in Neonates: The Influence of Ethical and Practical Issues on Design and Conduct  

**Additional Resources**

1) Platform Trials in Drug Development: Umbrella Trials and Basket Trials.  
2) Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs

3) Rare Diseases: Common Issues in Drug Development Guidance for Industry
FDA. 2019.

4) Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products
FDA. 2019.

5) Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices
FDA. 2016.

6) E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population
FDA. 2018.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11r1-addendum-clinical-investigation-medicinal-products-pediatric-population

7) Clinical Trials Guidance Documents

8) E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials: Guidance for Industry
FDA. 2021.

9) Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
FDA. 2020.

10) S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals
FDA. 2021.


Emphasizing Developmental Pharmacodynamics Biomarkers in PDD

Read this First


3) Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure FDA. 2021. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure


Helpful Explanation


Enhancing Research in Pediatric-Friendly Formulations

Read this First

1) Playing Hide and Seek with Poorly Tasting Paediatric Medicines: Do Not Forget the Excipients.

2) Making Medicines Baby Size: The Challenges in Bridging the Formulation Gap in Neonatal Medicine
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6600135/

3) Drug Formulations: Standards and Novel Strategies for Drug Administration in Pediatrics

4) Development of Paediatric Medicines: Points to Consider in Formulation
   https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex5TRS-970.pdf?ua=1
1) Advances in Drug Delivery Systems: Work in Progress Still Needed?
   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305387/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7305387/)

2) Formulation Approaches to Pediatric Oral Drug Delivery: Benefits and Limitations of Current Platforms
   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4673516/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4673516/)

3) Co-administration of Paediatric Medicines with Food and Drinks in the Context of Their Physicochemical Properties - A Global Perspective on Practices and Recommendations.
   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7056676/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7056676/)

   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7023035/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7023035/)

5) Sweetener Content and Cariogenic Potential of Pediatric Oral Medications: A Literature.
   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969777/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5969777/)

6) Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products: Safety Qualification of Excipients
   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771984/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771984/)

   [http://apps.who.int/iris/bitstream/handle/10665/273151/9789241514361-eng.pdf?ua=1](http://apps.who.int/iris/bitstream/handle/10665/273151/9789241514361-eng.pdf?ua=1)

8) Innovations in Pediatric Drug Formulations and Administration Technologies for Low Resource Settings
   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6835316/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6835316/)
1) Acceptability of Uncoated Mini-Tablets in Neonates--A Randomized Controlled Trial

2) Best Practice Recommendations Regarding the Assessment of Palatability and
   Swallowability in the Development of Oral Dosage Forms for Pediatric Patients

3) Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology
   Considerations
   FDA. 2019.
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-
   effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations

4) Bioavailability Studies Submitted in NDAs or INDs – General Considerations
   FDA. 2019.
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-studies-submitted-ndas-or-inds-general-considerations

5) Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations
   for Selection and In Vitro Methods for Product Quality Assessments
   FDA. 2018.
   https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-liquids-
   andor-soft-foods-vehicles-drug-administration-general-considerations-selection-and-vitro

6) Pharmaceutical Development of Medicines for Paediatric Use

7) Harnessing Formulation and Clinical Pharmacology Knowledge for Efficient Pediatric Drug
   Development: Overview and Discussions from M-CERSI Pediatric Formulation Workshop 2019

8) Pediatric Formulation Development - Challenges of Today and Strategies for Tomorrow:
   Summary Report from M-CERSI Workshop 2019
The Relevance of Pharmacoepidemiology Studies in Informing PDD

Read this First

1) Real-World Evidence to Assess Medication Safety or Effectiveness in Children: Systematic Review
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7221095/

2) Big Data in the Assessment of Pediatric Medication Safety
   https://pediatrics.aappublications.org/content/145/2/e20190562.long

3) Specifying a Target Trial Prevents Immortal Time Bias and Other Self-Inflicted Injuries in Observational Analyses
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5124536/

4) Framework for FDA’s Real World Evidence Program
   FDA. 2018.
   https://www.fda.gov/media/120060/download
Helpful Explanation

1) RWE for Regulatory Decision Making: List of Expert Documents and Resources on RWE from the International Society for Pharmacoepidemiology (ISPE) 
   https://www.pharmacoepi.org/strategic-initiatives/rwe-for-regulatory-decision-making/

2) An Inventory of European Data Sources for the Long-Term Safety Evaluation of Methylphenidate  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830128/

3) Causal Models and Learning from Data: Integrating Causal Modeling and Statistical Estimation  
   Petersen ML, van der Laan MJ. Epidemiology. 2014.  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4077670/

4) Development of a Neonatal Adverse Event Severity Scale Through a Delphi Consensus Approach  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6943241/

5) Assessment of Long-Term Neurodevelopmental Outcome Following Trials of Medicinal Products in Newborn Infants  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6848023/

   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8252086/

7) Pharmacoepidemiological Safety Studies in Children: A Systematic Review  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5111763/

8) Gene Therapy in Rare Diseases: The Benefits and Challenges of Developing a Patient-Centric Registry for Strimvelis in ADA-SCID  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889583/
9) Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies
FDA. 2012.

10) Rare Diseases: Natural History Studies for Drug Development
FDA. 2019.

11) Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
FDA. 2021.

Additional Resources

Public
1) World Federation of Hemophilia Gene Therapy Registry

2) Recommendations for the Design of Therapeutic Trials for Neonatal Seizures
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760680/

3) Development of a Retinopathy of Prematurity Activity Scale and Clinical Outcome Measures for Use in Clinical Trials
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6565513/

4) Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available
https://academic.oup.com/aje/article/183/8/758/1739860

Not Public
5) Pediatric Post-Marketing Safety Systems in North America: Assessment of the Current Status


How PK Modeling Can be Used to Inform Dosing

Read this First

1) A Pharmacokinetic Standard for Babies and Adults
   https://jpharmsci.org/article/S0022-3549(15)30935-7/fulltext

2) Physiologically-Based Pharmacokinetic Models for Children: Starting to Reach Maturation?

3) Physiologically Based Pharmacokinetic Modeling and Simulation in Pediatric Drug Development
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4260000/

4) Use of Modeling and Simulation in the Design and Conduct of Pediatric Clinical Trials and the
   Optimization of Individualized Dosing Regimens
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716585/

5) General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological
   Products
   FDA. 2014.
Helpful Explanation

1) Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007
https://jamanetwork.com/journals/jamapediatrics/fullarticle/1723817

2) Drugs and Lactation Database (LactMed)
https://www.ncbi.nlm.nih.gov/books/NBK501922

3) Brivaracetam Population Pharmacokinetics in Children with Epilepsy Aged 1 Month to 16 Years
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5423986/

4) General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products.
FDA. 2019.

5) Considerations in the Rational Design and Conduct of Phase I/II Pediatric Clinical Trials: Avoiding the Problems and Pitfalls

Additional Resources

1) Scientific Guidelines: Paediatrics

2) Clinical Lactation Studies and the Role of Pharmacokinetic Modeling and Simulation in Predicting Drug Exposures in Breastfed Infants

3) The Integration of Allometry and Virtual Populations to Predict Clearance and Clearance Variability in Pediatric Populations over the Age of 6 Years
The Role of Quantitative Systems Pharmacology in PDD

Read This First

1) Quantitative and Systems Pharmacology in the Post-Genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms. An NIH White Paper by the QSP Workshop Group
Rebecca Ward, editor. NIGMS. 2011.

2) History and Future Perspectives on the Discipline of Quantitative Systems Pharmacology Modeling and Its Applications
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027332/

3) A Six-Stage Workflow for Robust Application of Systems Pharmacology
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879472/

4) Systems Pharmacology
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113679/
5) Predictive Pediatric Modeling and Simulation Using Ontogeny Information  


Helpful Explanation

1) The Systems Biology of Drug Metabolizing Enzymes and Transporters: Relevance to  
   Quantitative Systems Pharmacology  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7292762/

2) Approaches to Dose Finding in Neonates, Illustrating the Variability between Neonatal Drug  
   Development Programs  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7408157/

3) Pharmacometrics and Systems Pharmacology for Metabolic Bone Diseases  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6533428/

4) Quantitative Systems Pharmacology Modeling of Acid Sphingomyelinase Deficiency and  
   the Enzyme Replacement Therapy Olipudase Alfa is an Innovative Tool for Linking  
   Pathophysiology and Pharmacology  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6063739/

5) Transitioning from Basic toward Systems Pharmacodynamic Models: Lessons from  
   Corticosteroids  
   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7058984/

6) How Does In Vivo Biliary Elimination of Drugs Change with Age? Evidence from In Vitro and  
   Clinical Data Using a Systems Pharmacology Approach  
   https://dmd.aspetjournals.org/content/44/7/1090.long
Additional Resources

1) A Survey of Neonatal Pharmacokinetic and Pharmacodynamic Studies in Pediatric Drug Development

2) Exposure-Response Assessment in Pediatric Drug Development Studies Submitted to the US Food and Drug Administration

3) Failed Pediatric Drug Development Trials

4) Quantitative systems pharmacology: a promising approach for translational pharmacology

5) Translational Quantitative Systems Pharmacology in Drug Development: from Current Landscape to Good Practices
   Bai JPF, Earp JC, Pillai VC. AAPS J. 2019.