### Thiopurines



- Thiopurines are purine analogs
- WHO List of Essential Medicine, among the most important medications needed in a basic health system
- Indications:
  - anti-cancer agents: acute lymphoblastic leukemia
  - Immunosuppresive agents: inflammatory bowel diseases (Crohn's disease and ulcerative colitis)

### Thiopurines are the Mainstay of ALL Therapy



- 6MP/6TG is the most important components of curative ALL therapy in children and adults
- Myelosuppression is the main side effect
- Dose titration is done based on WBC/ANC but challenging

   Too much dose reduction:
   less intense therapy, higher risk of relapse
   Too little dose reduction:
   excessive toxicities, treatment disruption, ALL relapse



### **Thiopurine Drug Metabolism**



#### Modified from Stocc et al *Clin Pharmacol Ther* 2009



#### **Human TPMT Gene and Mutant Alleles**



Proc Natl Acad Sci USA 1995, DNA Cell Bio 1996, Am J Hum Genet 1996, Clin Pharmacol Ther 1997 and 1998

### Hematological Toxicity Determined by TPMT genotype

#### Mercaptopurine Therapy Intolerance and Heterozygosity at the Thiopurine S-Methyltransferase Gene Locus

Mary V. Relling, Michael L. Hancock, Gaston K. Rivera, John T. Sandlund, Raul C. Ribeiro, Eugene Y. Krynetski, Ching-Hon Pui, William E. Evans **Memp** 



Relling et al., J Natl Cancer Inst 1999

6MP

TPMT

TGN

#### Meet Belinda, an Unexpected Case of 6MP toxicity



- P All standard risk
- B-ALL, standard risk

#### Two Loci Associated with 6MP Tolerance at Genome-wide Sig Level



- Discovery GWAS in COG AALL03N1 cohort (N=657), with independent validation (N=371)
- Illumina Exome array of 250K variants
- Each dot is a SNP and color indicates chromosome
- Inverse log-transformed P value on the Y axis, The taller the peak, the smaller the P value

#### NUDT15 C416T Variant is Strongly Associated with MP Intolerance





#### Cumulative Effects of NUDT15 and TPMT on 6MP Tolerance

=



Of patients requiring >80% dose reduction, 80% had risk variants at these two genes

Yang et al., J Clin Oncol 2015 (ALL) Yang et al., Nat Genet 2014 (IBD)

### NUDT15 Inactivates TGTP and Reduces Cytotoxicity

=



NUDT15 Diplotype and 6MP Metabolite (DNA-TG)



### NUDT15-guided Thiopurine Dose Adjustments?



#### Nudt 15-/- Mice Experienced Bone Marrow Suppression with DNATG Accumulation

=



- > We subsequently developed a syngeneic mouse leukemia with Nudt15 deficiency
- Thiopurine dose reduction in Nudt15<sup>-/-</sup> mice mitigated toxicity without compromising anti-leukemia efficacy

Nishii et al., **Blood** 2018

#### Dose Adjustment Based on Pharmacogenetics 13 Drugs with CPIC Recommendations

- *TPMT, NUDT15* 
  - MP, TG, azathioprine
- CYP2D6
  - Codeine, tramadol, hydrocodone, oxycodone, tricyclic antidepressant, tamoxifen, selective serotonin reuptake inhibitors, ondansetron, tropisetron, atomoxetine
- CYP2C19
  - tricyclic antidepressant, clopidogrel, voriconazole, selective serotonin reuptake inhibitors, proton pump inhibitors
- VKORC1
  - Warfarin
- CYP2C9
  - Warfarin, phenytoin, NSAIDs
- CYP4F2
  - Warfarin
- HLA-B
  - --Allopurinol, carbamazepine, Oxcarbazepine, abacavir, phenytoin
- HLA-A
  - carbamazepine

- CFTR
  - -- Ivacaftor
- DPYD
  - 5FU, capecitabine, tegafur
- G6PD
  - Rasburicase
- UGT1A1
  - Atazanavir
- SLCO1B1
  - Simvastatin
- IFNL3 (IL28B)
  - Interferon
- CYP3A5
  - Tacrolimus
- CYP2B6
  - Efavirenz
- RYR1, CACNA1S
  - Inhaled anesthetics
- *mtRNR1* (in progress)
  - aminoglycosides



#### 25 guidelines; 20 genes and > 60 drugs

#### Summary

- Pharmacogenomics seek to understand the genetic basis of interpatient variability in drug response.
- Pharmacogenetic variants can directly alter drug metabolism, efficacy, and toxicity in patients, with TPMT and NUDT15 as example in the context of thiopurine
- Thiopurine dosing can be individualized based on TPMT and NUDT15 genetics, highlighting the importance of pharmacogenetics in drug dosing
- Currently, there are 13 drugs for which dose adjustment is recommended based on pharmacogenetics, according to CPIC

### Acknowledgements



## CureSearch

Children's Oncology Group

Takaya Moriyama Chase Suiter Rina Nishii Ting-Nien Lin Wentao Yang Tomoya Isobe

Wenjian Yang

Mary Relling William Evans

**Biostatistics** Cheng Cheng Xueyuan Cao

**Oncology/Pathology** Ching-Hon Pui Hiroto Inaba











**JPLSG** Atsushi Manabe, Hiroki Hori, Motohiro Kato

**U Copenhagen** Kjeld Schmiegelow



**UNOP** Federico Antillon

**NUS** Allen Yeoh







National Institute of General Medical Sciences





## Developing a reasonable approach for pediatric dose selection:

### **Current and Future Approaches**





**Developing a reasonable approach for pediatric dose selection: Current and Future Approaches** 

Jeffrey S. Barrett, PhD, FCP Senior Advisor, Quantitative Medicine



#### Outline



### **Dose Selection Basics:**

- Data to make decisions
  - PK vs PK/PD
- Extrapolation

## **Current Approaches:**

- Top-down and bottom-up approaches
- Extrapolation
- Combination Approaches

## **Future Approaches:**

- Use of RWD
- Synthetic data approaches
- How good can we be
- Necessity of data integration and planning



- Dose Finding PK/PD
  - A target / endpoint is known or theorized based on adult or other data; dose-exposure to be defined
  - Studies designed to explore dose-response relative to endpoint target
- Equivalence Approach PK only (typically)
  - Exposure requirements based on adult experience "equivalent" safety and efficacy assumed by matching exposure
  - Studies designed to match exposure target

#### **Dose Selection Basics: PK/PD Approach**





Developmental changes, disease status and genetics

- Typically essential when adult experience and dose-exposure relationship is unlikely to be relevant for pediatric patients and/or adult endpoints are not relevant in children.
- The use of a PD endpoint that has been validated for use in children should be a prerequisite (often use an unvalidated marker with the adult endpoint as a comparator)

#### Dose Selection Basics: PK/PD Approach





 Requires prospective, dose-finding trials in the intended patient population (typically 3 or more doses – often just 2)

CRITICAL PATH

- Sensitive analysis techniques requiring only small blood samples should be used even with optimal sampling schemes
- All intended age strata of intended clinical use should be evaluated.
- Staggered dosing (older children first) often recommended.

Willmann, S., Thelen, K., Kubitza, D. et al. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. Thrombosis J 16, 32 (2018). https://doi.org/10.1186/s12959-018-0185-1

#### Dose Selection Basics: Equivalence Approach

- Emphasis is based on the assumptions that therapeutic exposures attained in adult patients are relevant (appropriate) for the intended pediatric patient population(s)
- Assumes that the underlying disease progressions are similar
- Sensitive analysis techniques requiring only small blood samples should be used even with optimal sampling schemes
- Designs are PK-centric without necessity of sampling for PD endpoints
- All intended age strata of intended clinical use should be evaluated.



CRITICAL PATH







Does a simple rule exist? NO  

$$Dose_{p} = Dose_{A} \times \frac{BW_{p}}{BW_{A}}$$
 Under-predicts across age strata  
 $Dose_{p} = Dose_{A} \times \frac{BSA_{p}}{BSA_{A}}$  Under-predicts infants and neonates  
 $Dose_{p} = Dose_{A} \times \left(\frac{BW_{p}}{BW_{A}}\right)^{0.75}$  Over-predicts age < 1y  
Conventional wisdom . . .?

"Scaling using body weight alone may be safer in the neonatal and infant age range in terms of avoiding toxicity: the possibility exists that an under-dose will be administered, but this dose can then be titrated up according to clinical response. Scaling using the BSA or BW<sup>0.75</sup> method would seem reasonable in children above 2 years of age, but even so should still be used with caution."

Johnson, T.N., The problems in scaling adult drug doses to children. Arch Dis Child, 2008. 93(3): p. 207-11

CRITICAL PATH

- The choice to use either method is typically based on the stage of development and the availability of adult data.
- The two approaches are complimentary and generally support each other
- Quite often, both are conducted

#### **Top-Down Approach:**

(Adult-informed PPK Model)

- Adult PPK model scaled to predict pediatric populations (size, maturation and ontogeny considerations)
- Simulations conducted to assess dose requirements across age / weight strata relative to adult experience (PK and/or PK/PD accommodated as needed)

#### **Bottom-Up Approach:**

(PBPK Model)

- Physiochemical and ADME data inputs to backbone of physiologic-represented model that can accommodate mechanistic relationship
- Not reliant on adult data but can use adult data to refine /qualify model.
- Can accommodate PK and/or PK/PD as well.
- Simulations conducted to assess dose requirements across age / weight strata relative to adult experience

- Evaluate doses or exposure profiles thought to yield equivalent exposures to adults
- 2. Estimate sample size to detect a difference in key parameters
  between treatment groups, adults or historical controls
- Select sampling scheme that will yield "meaningful" parameter estimates in children

- Generate PK distribution for intended age-weight subpopulations at all doses considered.
- Compare overlap in ranges across populations and age groups
- Compare with adult profiles
- Same as above.
- Derive metrics for individual simulated subjects (e.g., AUC, Cmax, CL)
- Compare groups via ANOVA
- Delta and variance to estimate sample size
- Define critical time points for PK parameters based on adult model – D-optimal design.
- Simulate pediatric profiles with various combinations of sampling time using pediatric-scaled model
- Re-fit simulated data; compare precision and bias





Scaling across age ranges . . . Customizing Expressions to Fit the Population

$$CL_{GRP} = CL_{STD} * \left[ \frac{W_{std}}{W_{std}} \right] * MF * OF * ???$$

 $CL_{GRP}$  is the group clearance

W<sub>i</sub> is the is the individual total body weight

 $CL_{std}$  is the clearance in a standardized individual of weight  $W_{std}$ 

MF = Maturation Function

OF = Organ Function

Patient-specific factors related to their care or treatment

CRITICAL PATH

#### Current Approaches: Bottom-Up Approach

*Picking Starting Doses – the usual procedure* 





Zhao P. et al., Clin Pharmacol Ther, 2011

#### **Current Approaches: Bottom-Up Approach** *Picking Starting Doses – the usual procedure*

#### Approach:

- Incorporate physiochemical and ADME data into PBPK model framework; refine with in vivo data (adult and /or pediatric data if available).
- Devise dosing and sampling scenarios consistent with planned study constructs.
- Recommend scenarios with highest PTOS.
- Evaluate /refine against real-time, actual study data if possible.



Willmann S, Thelen K, Kubitza D, Lensing AWA, Frede M, Coboeken K, Stampfuss J, Burghaus R, Mück W, Lippert J. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. Thromb J. 2018 Dec 4;16:32. doi: 10.1186/s12959-018-0185-1. PMID: 30534008; PMCID: PMC6278136.

#### **Future Approaches** Use of RWD – Value for Prescribing and Design of Future Trials





- Both from the standpoint of guiding dosing practice and designing or complementing clinical trials, RWD has become and valued asset.
- As pediatric research and development often operates with a deficit of data and relies heavily on the adult experience, there is great perceived opportunity.

#### **Future Approaches**

Use of RWD – Still a few caveats





Figure 2. Overcoming the Barriers to using Real World Data to Achieve Optimized Dosing for Children.

Currently, pediatric dosing relies on mg/kg calculations. In order to use real world data (RWD) to achieve optimized pediatric dosing, several barriers must be overcome.

Developing reliable algorithms and establishing standardized data processing will assist in overcoming these barriers.

Van Driest SL and Choi L. Real World Data for Pediatric Pharmacometrics: Can We Upcycle Clinical Data for Research Use? Clin Pharmacol Ther. 2019 July ; 106(1): 84–86. doi:10.1002/cpt.1416.

- For many drugs valid measures of drug effect are not consistently documented (e.g., therapeutic response to medications for attention deficit hyperactivity disorder or depression) or not available for the full spectrum of pediatric patients.
- Across all drugs, reliable documentation of adverse drug events is incomplete and represents an area of need for complete PD analysis. Longterm funding for multi-site collaborative networks is required to address the challenges, pool data, and validate findings.
- Generation of high-quality, generalizable, and validated data will facilitate subsequent clinical implementation.

## **QSP** Modeling Application: Used in ERT program for extrapolation to

#### pediatrics: Olipudase Example

- Quantitative systems pharmacology (QSP) is a mechanistic modelling tool that links molecular mechanisms of disease and drug to biomarkers and clinical endpoints used for assessment of disease and therapeutic effect
- QSP is suited to understanding the system-level response to treatment across multiple PD markers and clinical endpoints, and to assessing patient variability on a mechanistic basis

•

٠

The QSP model for olipudase alfa links a reduced-order physiologically based pharmacokinetic (PBPK) model with molecular-, cellular-, and organlevel sub-models to understand treatment response patterns



#### Figure 1, CPT Pharmacometrics Syst. Pharmacol. (2018)

Kaddi CD, Niesner B, Baek R, Jasper P, Pappas J, Tolsma J, Li J, van Rijn Z, Tao M, Ortemann-Renon C, Easton R, Tan S, Puga AC, Schuchman EH, Barrett JS, and Azer K. Quantitative Systems Pharmacology Modeling of Acid Sphingomyelinase Deficiency and the Enzyme Replacement Therapy Olipudase Alfa Is an Innovative Tool for Linking Pathophysiology and Pharmacology. CPT Pharmacometrics Syst Pharmacol. 2018 Jul; 7(7): 442–452. PMCID: PMC6063739, PMID: 29920993 17

#### Pediatric extrapolation: Leveraging PBPK-QSP for Disease and Response Similarity Assessment – Olipudase Example (ASMD)

Critical elements for pediatric extrapolation:

- Selection of clinical endpoints or biomarkers for tracking disease: organ and sub-organ levels (multiscale)
- Genotype-phenotype mapping to create virtual populations commensurate with disease severity levels, substantiated by registry data
- Virtual population can be genotype-prevalence weighted, based on registry prevalence distribution
- Multi-organ/biomarker integration through model is critical to bridge together a multi-parameter distribution relationship

Sampling of residual enzyme activity distributions to represent each cohort (adults, pediatrics with different disease severity spectra or genotypes

PD variability relative enzyme expression levels from mRNA expression data PK variability clearance, absorption rate constant, central volume, and bioavailability



Hypothetical pediatric scenarios



#### Virtual ASMD Patients



#### **Future Approaches** *Synthetic data approaches*

#### **Approach and Rationale:**

- Privacy restrictions limit access to protected patient-derived health information for research purposes.
- Data anonymization is required to allow researchers data access for initial analysis before granting institutional review board approval.
- Synthetic data generation seeks to mimic data from real electronic medical records, providing a synthetic patient dataset to analyze.





#### **Planning**

- Starts at the Early Development teams and the TPP
- Empower the pediatric section with key deliverables around dose projection
- Obligate the PSP and PIP to include these deliverables
- Delegate to the right skillsets.

#### **Data Integration**

- Landscape analysis on key data elements
  - Include RWD (prevalence, SOC, competitive intelligence data
  - Purchased data sources, literature data assembly
- Generation of analysis datasets in advance of use
- Scripting and coding templates where possible

# CRITICAL PATH

#### Future Approaches How good can we be?

- Safety should still guide us give a safe dose first
- Still a disconnect between the prescription and the dosing
- Plan for RWD evolution to influence precision dosing approaches in the future
- Still need flexibility in the pediatric formulations themselves
- The tools we leave behind from the effort to get the dose right in children become the starting point for model-informed precision dosing (MIPD) algorithms – hopefully, our future.

### We just need to be better!



Weight	Motrin Milligram Dosage	Motrin Infant drops 50mg/1.25ml	Motrin Children's liquid 100mg/5ml	Motrin Chewables 50mg each	Motrin Junior 100mg each
12 - 17 lbs	50 mg	1 dropper (1.25 ml)	½ tsp (2.5 ml)	N/A	N/A
18 - 23 lbs	75 mg	1 ½ dropper (1.875 ml)	3/4 tsp (3.75 ml)	N/A	N/A
24 - 35 lbs	100 mg	2 droppers (2.5 ml)	1 tap (5 ml)	2 tablets	1 tablet
36 – 47 lbs	150 mg	3 droppers (3.75 ml)	1 ½ tsp (7.5 ml)	3 tablets	1 % tablet
48 - 59 lbs	200 mg	N/A	2 tsp (10 ml)	4 tablets	2 tablets
60 - 71 lbs	250 mg	N/A	2 ½ tsp (12.5 ml)	5 tablets	2 ½ tablets
72 - 95 lbs	300 mg	N/A	3 tsp (15 ml)	6 tablets	3 tablets

#### **References:**



- Germovsek E, Barker CIS, Sharland M, Standing JF. Pharmacokinetic-Pharmacodynamic Modeling in Pediatric Drug Development, and the Importance of Standardized Scaling of Clearance. Clin Pharmacokinet. 2019 Jan;58(1):39-52. doi: 10.1007/s40262-018-0659-0. Erratum in: Clin Pharmacokinet. 2018 Dec 17;: PMID: 29675639; PMCID: PMC6325987.
- De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol. 2011 May;67 Suppl 1(Suppl 1):5-16. doi: 10.1007/s00228-009-0782-9. Epub 2010 Mar 26. PMID: 20340012; PMCID: PMC3082690.
- Willmann, S., Thelen, K., Kubitza, D. et al. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. Thrombosis J 16, 32 (2018). <u>https://doi.org/10.1186/s12959-018-0185-1</u>
- Reiner Benaim A, Almog R, Gorelik Y, Hochberg I, Nassar L, Mashiach T, Khamaisi M, Lurie Y, Azzam ZS, Khoury J, Kurnik D, Beyar R. Analyzing Medical Research Results Based on Synthetic Data and Their Relation to Real Data Results: Systematic Comparison From Five Observational Studies. JMIR Med Inform 2020;8(2):e16492, DOI: 10.2196/16492, PMID: 32130148, PMCID: 7059086
- Van Driest SL and Choi L. Real World Data for Pediatric Pharmacometrics: Can We Upcycle Clinical Data for Research Use? Clin Pharmacol Ther. 2019 July ; 106(1): 84–86. doi:10.1002/cpt.1416.
- Mulugeta LY, Yao L, Mould D, Jacobs B, Florian J, Smith B, Sinha V, Barrett JS. Leveraging Big Data in Pediatric Development Programs: Proceedings From the 2016 American College of Clinical Pharmacology Annual Meeting Symposium. Clin Pharmacol Ther. 2018 Jul;104(1):81-87. doi: 10.1002/cpt.975. Epub 2018 Jan 10. PMID: 29319159.
- Kaddi CD, Niesner B, Baek R, Jasper P, Pappas J, Tolsma J, Li J, van Rijn Z, Tao M, Ortemann-Renon C, Easton R, Tan S, Puga AC, Schuchman EH, Barrett JS, and Azer K. Quantitative Systems Pharmacology Modeling of Acid Sphingomyelinase Deficiency and the Enzyme Replacement Therapy Olipudase Alfa Is an Innovative Tool for Linking Pathophysiology and Pharmacology. CPT Pharmacometrics Syst Pharmacol. 2018 Jul; 7(7): 442–452. PMCID: PMC6063739, PMID: 29920993
- Barbour AM, Fossler MJ, Barrett J. Practical considerations for dose selection in pediatric patients to ensure target exposure requirements. AAPS J. 2014 Jul;16(4):749-55. doi: 10.1208/s12248-014-9603-x. Epub 2014 May 20. PMID: 24841797; PMCID: PMC4070253.



## jbarrett@c-path.org



# Current and Future Pediatric Dosing Considerations from a Regulatory Viewpoint

Lynne P. Yao, M.D. Director, Division of Pediatric and Maternal Health Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) Office of New Drugs Center for Drug Evaluation and Research U.S. FDA

## **Disclosure Statement**



I have no financial relationships to disclose relating to this presentation

• The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

# U.S. Evidentiary Standard for Approval



- For approval, pediatric product development is held to same evidentiary standard as adult product development:
- A product approved for children must:
  - Demonstrate substantial evidence of effectiveness/clinical benefit (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease
- Evidence of effectiveness [FD&C 505(d) (21 U.S.C. § 355(d)].
  - Evidence consisting of adequate and well –controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling
- Adequate safety information must be included in the application to allow for appropriate risk benefit analysis [FD&C 505(d)(1)]

# Special Considerations for Pediatric Product Development



- Ethical considerations
  - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
  - Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be "low"
  - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
  - Ethical considerations do play a role in the need to correctly apply pediatric extrapolation
- Feasibility considerations
  - The prevalence and/or incidence of a condition is generally much lower compared to adult populations

# Statutory Requirement



- Pediatric Research Equity Act (PREA) requires that a pediatric assessment "shall contain data. . .to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective." [505B(a)(2)(A)(ii)]
- No clear requirement to establish an "optimal" dose
- Unsuccessful dose selection methods lead to failed pediatric trials

# Extrapolation of Efficacy: Disease/response "similarity" is a continuum



Different	Dissimilar	Similar	Same
No overlap between adult and pediatric condition	Some degree of overlap with significant differences between adult and pediatric condition	Large degree of overlap with some differences between adult and pediatric condition	Significant overlap; no known significant differences between adult and pediatric condition

Increasing relevance of adult information to pediatric population with increasing confidence in similarity between adult and pediatric condition

Pediatric RCT(s)

Pharmacodynamic markers, Bayesian methodologies, etc.

Exposure matching

# Apparent Exposure Response in Pediatrics



- Pediatric exposure response studies are difficult to design to truly evaluate exposure response
  - Ethically difficult to assign patients to a dose that would be considered "ineffective"
  - Assignment to one dose in the effective range ("flat part") of the curve may lead to incorrect conclusions about differences in exposure response
  - Consider evaluation of dose-response or "dose-exposure-response"
- Use of biomarkers to better understand response and guide dose selection

## **Pediatric Dose Selection Scenarios**

### Assume similar dose-exposureresponse (DER) compared to adults

- Requires confidence in DER in adults
- Methods used to match exposures will depend upon age groups to be studied
- Confirmation of model-based predictions is needed

### Cannot assume similar doseexposure-response (DER) in adults

- Will need to conduct dose-ranging studies
- May use PK/PD modeling but will need to have PD marker available
- Generally will need evaluation of the PD marker in adult populations
- Confirmation of dose regardless of method of selection will also be needed

# Incorporation of Available Data





## A Regulator's Perspective

- Takes more time
- Requires early planning
- Difficult to obtain in certain age groups
- Ultimately could support more streamlined approaches

- Takes less time
- Often includes
   numerous assumptions
- False assumptions will lead to incorrect conclusions
- More difficult to obtain regulatory acceptance



# Summary



- Our goal is to increase the availability of approved products for use in pediatric patients
- Dose selection in pediatric development programs depends upon the available knowledge
- Optimizing the use of available data
  - Appropriate use of modeling and simulation
  - Transparency in model development and confirmation
  - Innovative statistical approaches
  - Appropriate use of biomarkers
- Improved communication of dosing information in labeling



## Thank you



## Pediatric Dose Selection FDA/MCERSI Workshop – Wrap Up

Gilbert J. Burckart, Pharm.D. Associate Director for Pediatrics Office of Clinical Pharmacology OTS, CDER, FDA

Disclaimer: The comments and concepts presented are those of the speaker and should not necessarily be interpreted as the position of the US FDA

## Thanks!



- Many thanks again to:
  - All of the speakers who gave their time and effort to make the workshop a success!
  - The University of Maryland Center for Excellence in Regulatory Science and Innovation (MCERSI)
  - The US FDA Office of Clinical Pharmacology
- What comes next?



The future challenge is to create a structured approach to determining pediatric doses for new therapeutic agents (CPT Commentary, 2010) - This workshop is a step in the direction of developing a structured approach.

### Workshop Published Supplement – The Journal of Clinical Pharmacology, March 2021

Guest Editors: John van den Anker, Gilbert Burckart

- Aaron Pawlyk A Call for Objective Dose Selection to Increase
   Success in Pediatric Clinical Trials
- •
- Gil Burckart/John van den Anker A Decision Tree for Pediatric Dose Selection – Workshop Summary
- John van den Anker Dose Selection for Premature Infants
- •
- Gil Burckart Methods Used for Pediatric Dose Selection in Drug Development Programs Submitted to the US FDA 2012-2019
- •
- Efthymios Manolis The EMA experience with pediatric dose selection
- •
- Alice Ke PBPK modeling and allometric scaling in pediatric drug development: where do we draw the line?
- •
- Joga Gobburu Pediatric Therapeutics Management with Clinical Decision Support Systems
- •
- Hao Zhu Confirming Extrapolation of Efficacy: Atypical Antipsychotic Dose-Selection in Adolescents with Schizophrenia and Bipolar I Disorder
- •
- Youwei Bi Use of MIDD in Dose Selection in Pediatric Clinical Trials
- •
- Jian Wang Evaluation of Exposure-Response Similarity Between Pediatrics and Adults in Drug Development

- Bernd Meibohm Pediatric Dose Selection for Therapeutic Proteins
  - Denne Caralas, Dadiateia Dena Dena lataratia
- Danny Gonzalez Pediatric Drug-Drug Interaction Evaluation: Drug, Patient Population, and Methodological Considerations
- •
- Mona Khurana Renal Impairment Dosage Recommendations for Pediatric Patients
- •
- Andre Dallmann Pediatric Drug Absorption and Physiologically-Based Pharmacokinetic Modeling
- •
- Andre Dallmann Predictive performance of PBPK dose estimates for pediatric trials
- •

.

.

- Jun Yang The Role of Pharmacogenomics in Drug Dosing in Children
- Jeff Barrett Precision Dosing in Children
  - . .
- Sander Vinks Model-informed Pediatric Dosing
- Karel Allegaert Dose related adverse drug-related events in neonates: severity assessment and recognition
- - Gil Burckart The Role of Drug Safety in Pediatric Dose Section

