2025 Mechanistic Modeling Workshop

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Shaping the Path Forward: Advancing Mechanistic Models for Regulatory Use

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(October 2025)

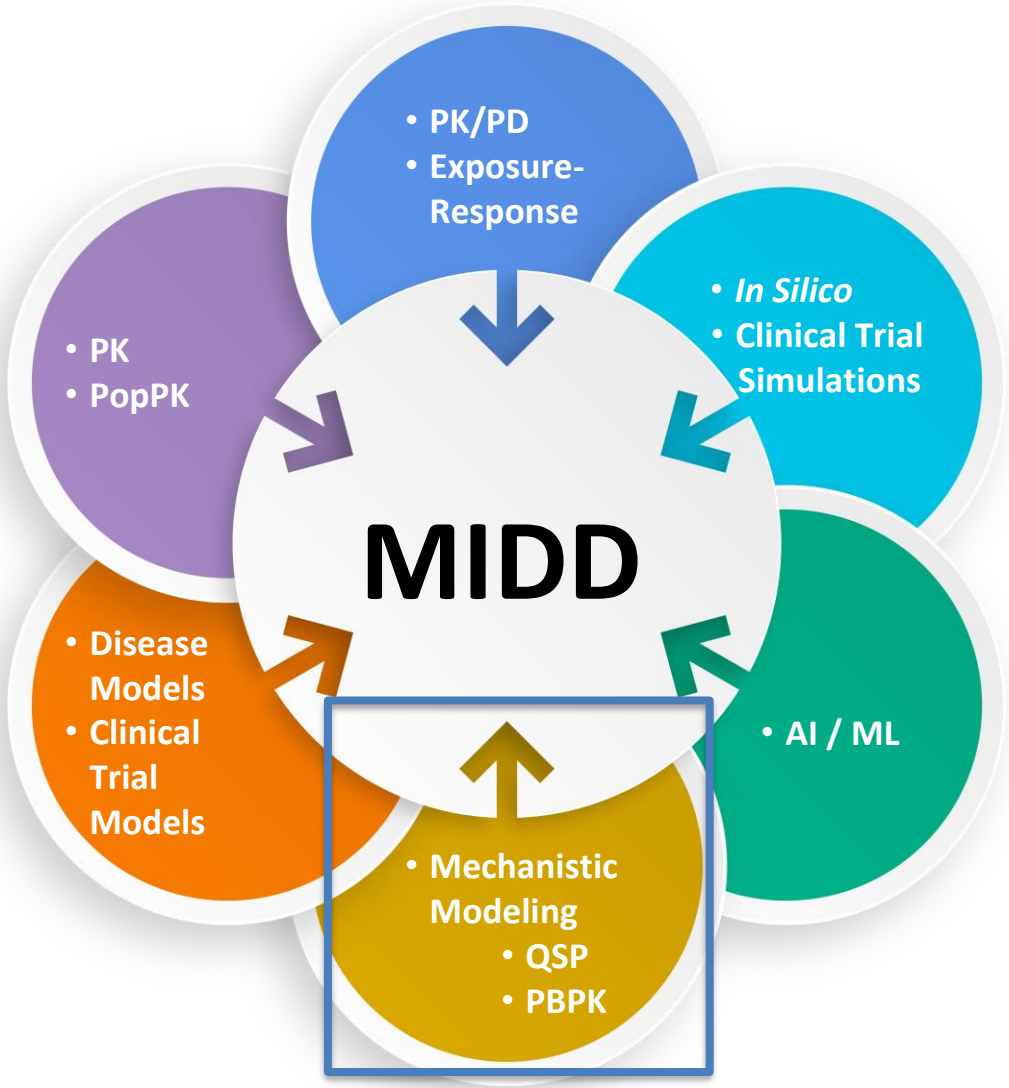
Disclaimer: This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Outline

- Introduction
  - MIDD & Mechanistic Modeling
  - Guidance
  - Roles of Mechanistic Modeling
- Mechanistic Reviews at the FDA
  - Submission and Review of PBPK Modeling
  - Submission and Review of QSP Modeling
  - Review Case for Olipudase Alpha
- Challenges and Opportunities for Mechanistic Modeling
- Take Home Messages

MIDD and Mechanistic Modeling

MIDD is defined as the strategic use of computational modeling and simulation (M&S) methods that integrate nonclinical and clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence*

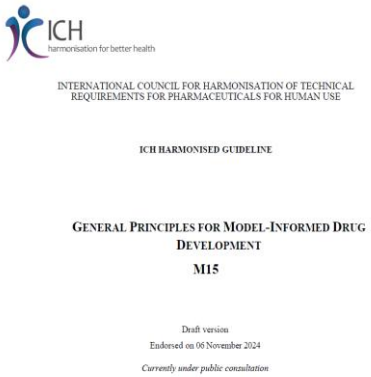


To Streamline Drug Development and Enhance Patient Care

* ICH M15: General Principles for MIDD

Courtesy by Huang SM 2019 AAPS

Guidance on Mechanistic Modeling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ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG DEVELOPMENT

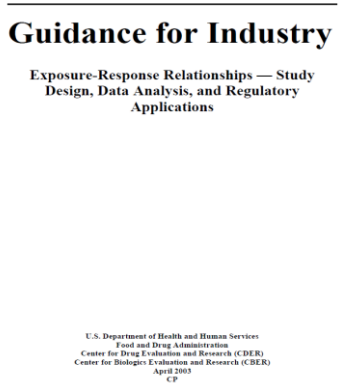
M15

Draft version

Endorsed on 06 November 2024

Currently under public consultation

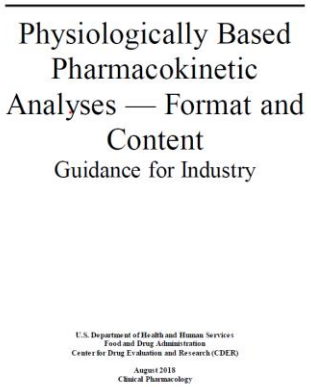
General Principles for MIDD


Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 2003
CP

Exposure-Response Relationship

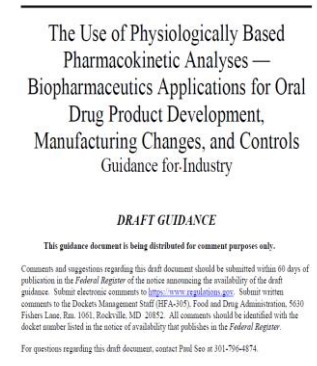

Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology

Format & Content for PBPK


The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Paul Seo at 301-796-4874.

PBBM

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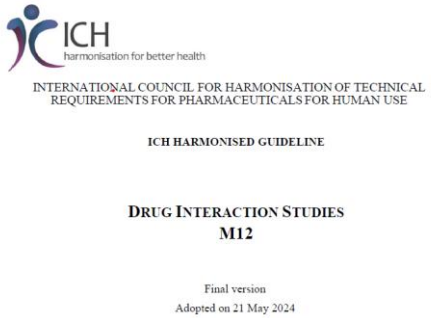
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ICH HARMONISED GUIDELINE

DRUG INTERACTION STUDIES

M12

Final version

Adopted on 21 May 2024

Drug-Drug Interaction


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PEDIATRIC EXTRAPOLATION

E11A

Final version

Adopted on 21 August 2024

Pediatric Extrapolation


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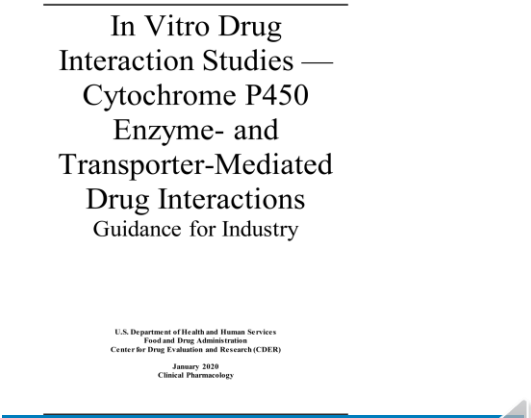
BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

M13A

Bioequivalence


In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2020
Clinical Pharmacology

Drug-Drug Interaction

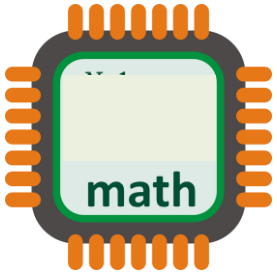
Roles of Mechanistic Modeling

Drug Product

- Release characteristics
  - Oral, IM, transdermal, locally acting
- Absorption

Patients

- Translational findings
- Disease characteristics
- Patient features
  - Subgroups
  - Subtypes
- Pharmacokinetics
  - ADME
- Pharmacodynamics
  - Biomarkers
- Clinical outcomes



Mechanistic Modeling

- Product quality standards
  - Dissolution specs
- Bridging strategy
  - Bioavailability and Bioequivalence
- Administration
  - Food effect, injection sites, alcoholic beverages
- Dosing with extrinsic factors
  - DDIs (proton pump inhibitors, CYP or transporter inhibitors, inducers)
- Dosing with Intrinsic factors:
  - Organ impairment, maturation, and aging
- Indication extrapolation
- NAM (support FIH trials)
- System toxicology
- Dose selection
- Clinical trial design
- Evidence generation
- Endpoint selection
- Biomarker / pharmacodynamics tool development

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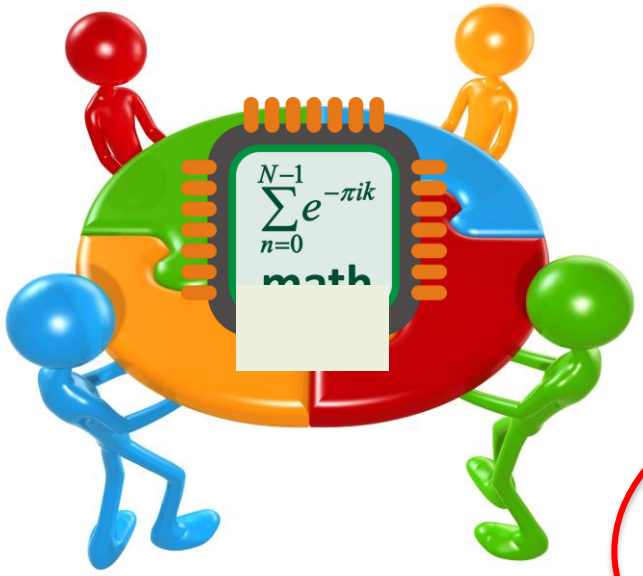
Mechanistic Modeling Function

Product Quality Control

Generic Products Development



Mechanistic Modeling

Cell and Gene Therapy Development

New Drug Development

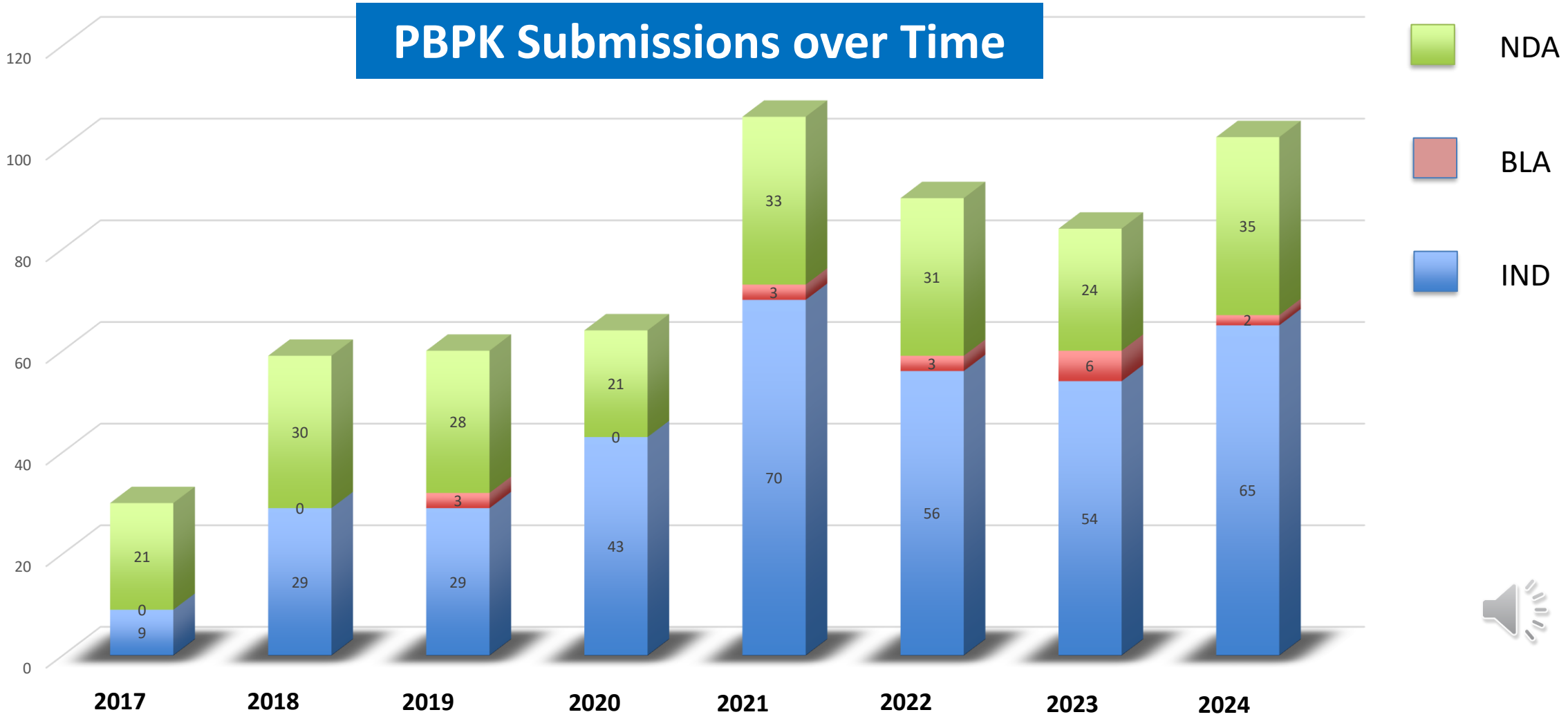
Support & Collaboration

Computational Power

System Biology

Joint efforts in Scientific Community

Summary of PBPK Submissions



Regulatory Application & Predictive Performance

- Higher confidence, greater experience, fewer knowledge gaps, higher likelihood of acceptability
- Some experience, knowledge gaps identified, likelihood of acceptability on case-by-case basis
- Limited experience, significant knowledge gaps, low likelihood of acceptability at this time

Drug Interactions

CYP450 *Drug as Substrate*

- Inhibitor interaction prediction with higher potency clinical data verification
- Some experience with dual enzyme time dependent inhibitor and inducer prediction, but knowledge gaps exit

CYP450 *Drug as Perpetrator*

- Negative interaction prediction for inhibition
- Some experience with positive interaction prediction on CYP3A pathway, but knowledge gaps exist
- Some experience with interaction prediction for induction on CYP3A pathway, but significant knowledge gaps exist on the in vitro/in vivo extrapolation of induction data

Transporter Systems

- Some experience with P-gp and combined P-gp/ CYP3A interaction prediction, but knowledge gaps exist
- Some experience with negative interaction prediction on intestinal BCRP and renal OATs, but knowledge gaps exist
- Hepatic OATP1B1/3, NTCP, MRP2, and renal MATEs and OCT2 interaction prediction is not mature. Potential for combining endogenous biomarker data

FDA Phase II Metabolism

- Some experience with UGT for negative interaction prediction, but knowledge gaps exist

Specific Populations

Pediatrics

- Some experience, but knowledge gaps exist

Renal or Hepatic Impairment

- Very few RI submissions and the available PBPK submission did not provide adequate validation
- Some HI experience, but model performance varies.

Pregnancy, Lactation, Ethnicity, Geriatrics, Obesity, & Disease States

- Some pregnancy experience, but knowledge gaps exist
- Prediction for lactation & other intrinsic factors not mature

Other Areas

Food, formulation, & tissue concentration

- Some tissue concentration experience but need to review case-by-case
- Limited gastric emptying time experience with GLP-1 mediated gastric empty delay
- Limited formulation experience, limited to negative prediction and knowledge gaps exist
- Food effect prediction is not mature for positive interaction

pH effect on Fa

- Some experience, limited to negative prediction

Absorption

- BCS Class I drugs
- Some experience with BCS Class II, but knowledge gaps exist
- BCS Class III and IV prediction not mature

Courtesy from Dr. Yuching Yang and Joseph Grillo

Selected Case Example for PBPK Modeling

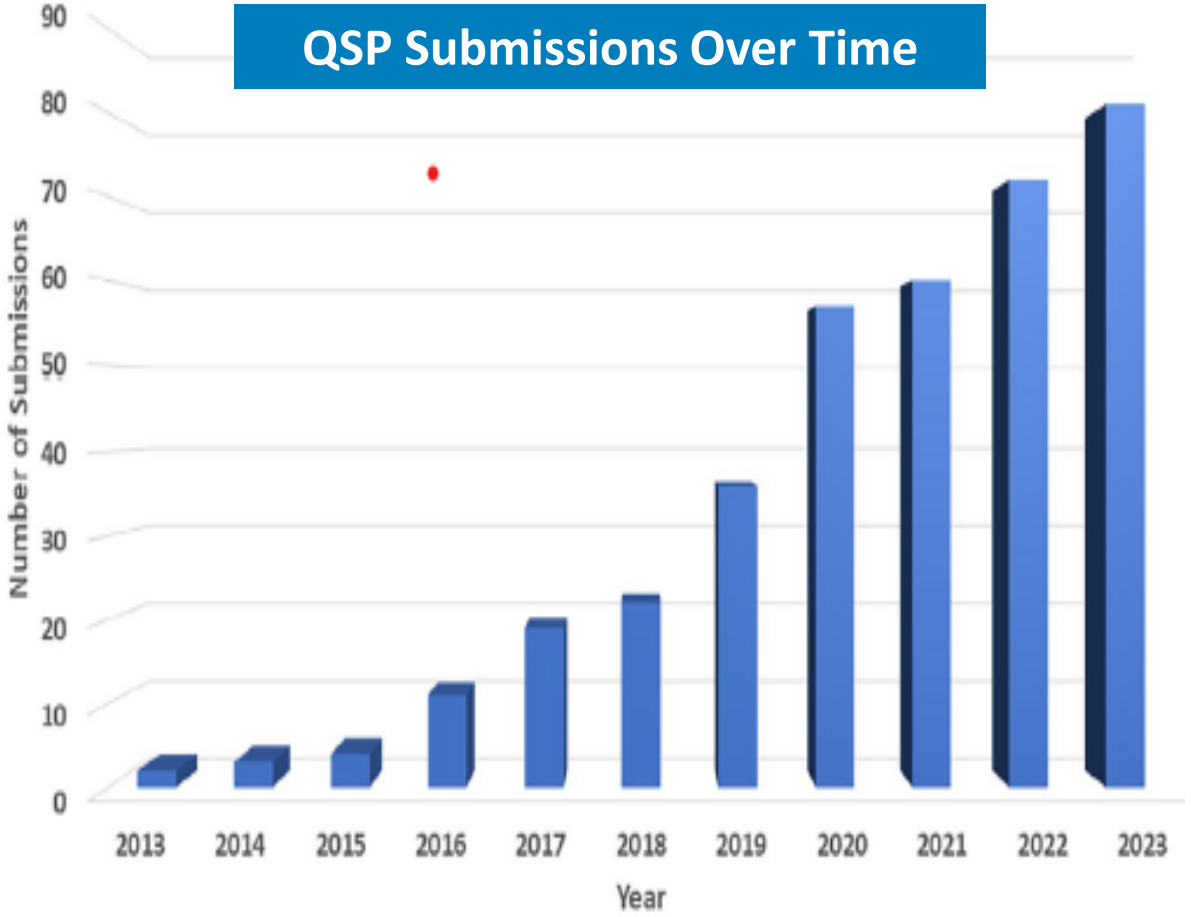
Area of application	Drug (example)	PBPK summary
Complex DDI	Apalutamide[1]	Predict and inform DDI dosing recommendations for apalutamide, which has an active metabolite and is a dual substrate of CYP2C8 and CYP3A
Pharmacogenetics -DDI	Eliglustat[2]	Predict and inform DDI dosing recommendations in patients with different CYP2D6 phenotypes receiving concomitant CYP inhibitors
Transporter DDI	Mobocertinib[3]	Predict the effect of mobocertinib on the PK of P-gp substrates (digoxin, and dabigatran)
	Cabotegravir and rilpivirine[4]	Predict the effect of cabotegravir on the PK of OAT1 and OAT3 substrates
Pediatric	Solifenacin[5]	Predict and inform the selected pediatric equivalent doses (PEDs) in USPI
	Risdiplam[6]	Predict the effect risdiplam on the PK of a sensitive CYP3A substrate (midazolam) in children 2 months to 18 yrs of age
Hepatic Impairment	Olanzapine and samidorphan[7]	Predict the effect of hepatic impairment on the exposure of orally administered samidorphan by leveraging limited clinical data collected in different dosing route
	Adagrasib[8]	Predict the effect of hepatic impairment on the steady-state exposure adagrasib in patients
Absorption factor	Tirzepatide[9]	Predict the effect of tirzepatide on the pharmacokinetics of a range of small molecules as a results of gastric emptying
	Asciminib[10]	Predict the effect of elevated gastric pH on the PK of asciminib at a higher dose level

1 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210951Orig1s000MultidisciplineR.pdf
2 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf
3 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215310Orig1s000MultidisciplineR.pdf
4 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/212887Orig1s000,212888Orig1s000IntegratedR.pdf
5 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/209529Orig1s000ClinPharmR.pdf
6 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213535Orig1s000TOC.cfm
7 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213378Orig1Orig2s000MultidisciplineR.pdf
8 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216340Orig1s000TOC.cfm
9 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215866Orig1s000ClinPharmR.pdf
10 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215358Orig1s000,Orig2s000MultidisciplineR.pdf

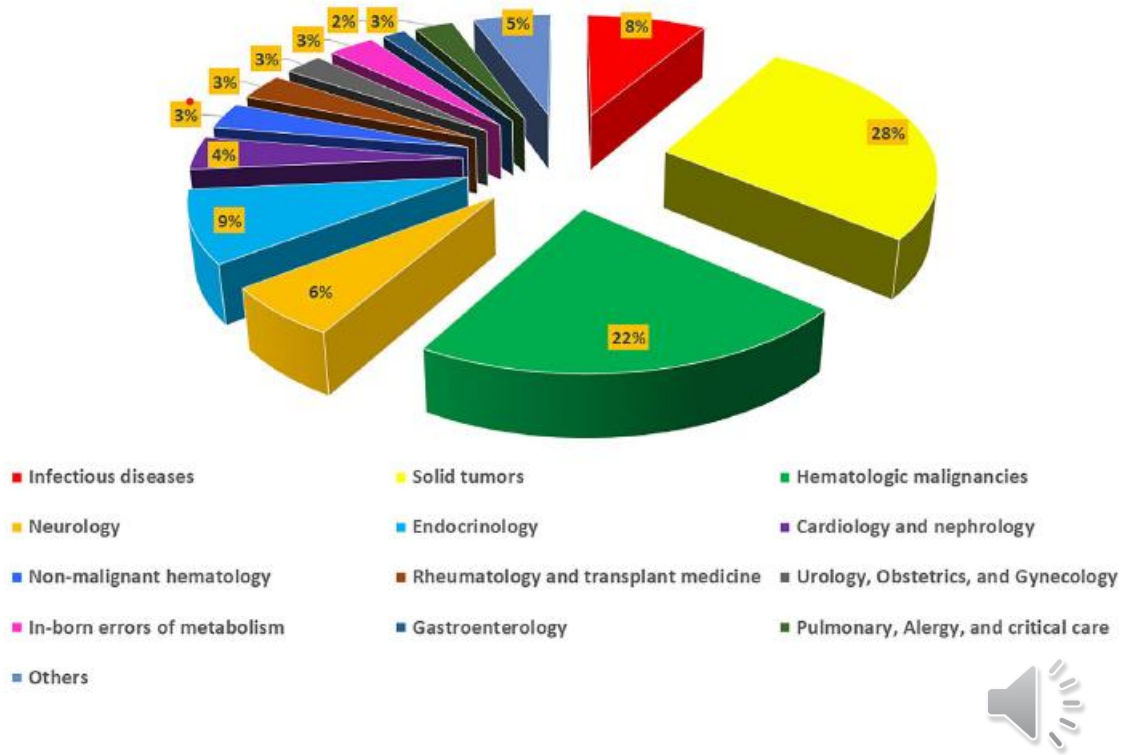
Courtesy from Dr. Yuching Yang

Summary of QSP Submissions

QSP Submissions Over Time



QSP Submissions by Therapeutic Areas



Bai et al. 2024 Dec;13(12):2102-2110. doi: 10.1002/psp4.13208

Case Examples for QSP Modeling

Compound Name	Value of QSP Modeling
Olipudase Alpha	Indication: Non-CNS CAMD in adult and pediatric patients Value: Supportive evidence for pediatric extrapolation by demonstrating similarity in disease progression and drug response between adult and pediatric extrapolation.
Nirmatrelvir + Ritonavir	Indication: COVID-19 at high risk for progression. Value: Hypothesis generation for the necessity of further dose optimization in patients with compromised immune response.
Drug X	Intended Indication: Oncology. Value: Evidence on potential efficacy and safety based on In vitro findings (due to human specific targets) for the determination of MABEL dose and safety margin and further dose selection in First-In-Human trials.
Drug Y	Intended Indication: Oncology. Value: Dose optimization for original set-up dosing and maintenance dosing for Phase 3 trial design

Olipudase Alpha Review

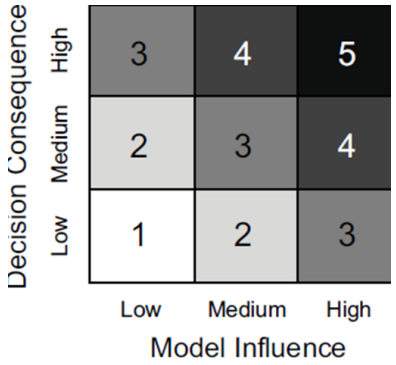
Olipudase Alpha

Enzyme replacement therapy for non-CNS manifestation of acid sphingomyelinase deficiency (ASMD) in pediatric and adult patients.

- ✓ **Autosomal recessive disease caused by pathogenic variants in SMPD1 gene**
- ✓ **Deficiency in acid sphingomyelinase (ASM) causing accumulation of sphingomyelin (SM)**
- ✓ **Incidence 0.4 to 0.6 per 100,000 birth**
- ✓ **Symptoms observed from infancy to adulthood**
- ✓ **Hepatosplenomegaly, deterioration in lung function, liver disease and growth delays**

QOI: Can the QSP model support the similarity in disease progression and treatment response between pediatric and adult ASMD patients to support pediatric extrapolation?

- Risk-based evaluation approach

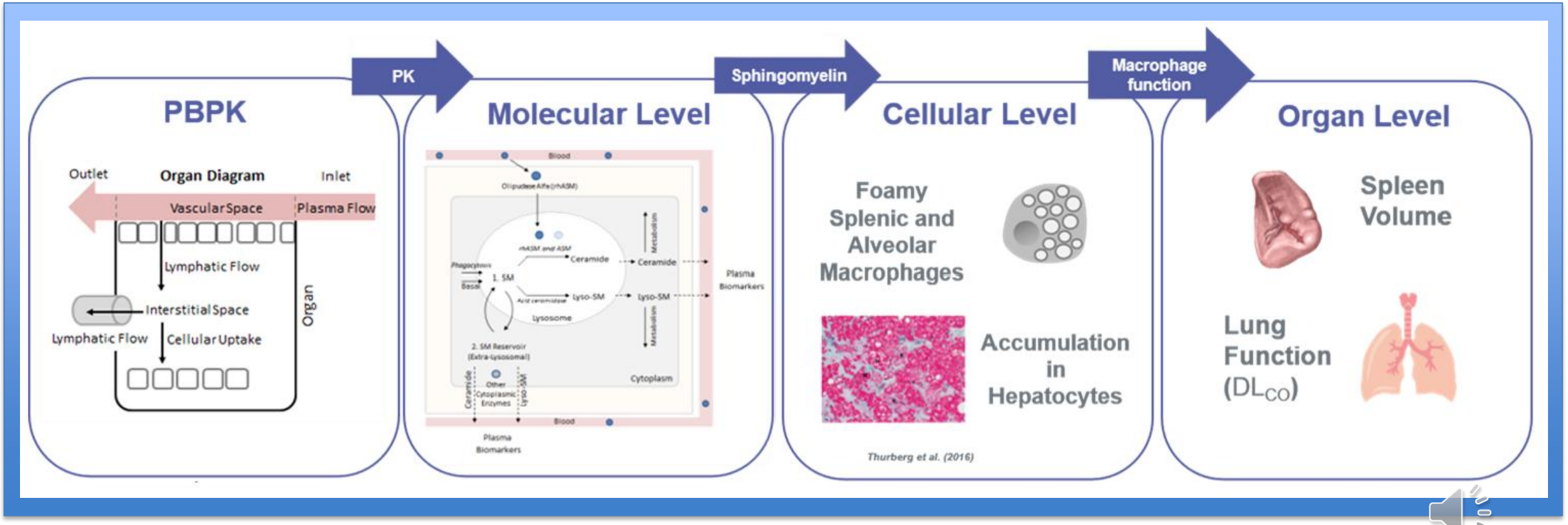


Subsequent model evaluation should be consistent with the model risk.

* The review process is still evolving as we accumulate more experience.

Model Structure Reflects the Biological Process

Muti-scale QSP model that describes key pathophysiology of ASMD and MOA of olipudase alfa



From https://cersi.umd.edu/sites/cersi.umd.edu/files/2-4_Session2_SusanaZaph_final.pdf

Courtesy from Dr. Yuching Yang

Various Sources of Data Informing the QSP Model

Modeling stage	Study	Description	QSP modeling parameters obtained
Development	3.2.S.3.1	**Nonclinical** data	**Molecular and cellular** sub-model parameters (i.e., k_{cat} and K_M for olipudase alfa)
Development	03-0380Pnp	**Preclinical** data	**PBPK** sub-model parameters (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	02-0266Pnp	**Preclinical** data	**PBPK** sub-model parameters (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	03-0142Pnp	**Preclinical** data	**PBPK** sub-model parameters (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	05-0094Pnp	**Preclinical** data	**PBPK** sub-model parameters (i.e., Lymphatic flow rate; organ vascular reflection coefficient)
Development	SPHINGO-001-00	**Natural History study**	**Spleen** sub-model parameters (i.e., maximum spleen volume)
Development	SPHINGO-006-05	**Phase 1a** clinical trials (Adult ASMD patients, SD, 0.03, 0.1,0.3,0.6 and 1.0 mg/kg)	**Molecular and cellular** sub-model parameters (i.e., Rate of transit of ceramide; rate of SM exchange; rate of export of ceramide into plasma)
Development/ Validation/ Refinement	DFI13412	**Phase 1b** clinical trials (Adult ASMD patients, Intrapatient dose escalation 0.1- 0.3- 0.3- 0.6- 1.0- 2.0 and -3.0 (target) mg/kg, Q2W, 26 weeks)	**PBPK** sub-model parameters (i.e., Organ vascular reflection coefficient) **Molecular and cellular** sub-model parameters (i.e.,Number of ASM, acylSMase molecules per cell; rate of olipudase alfa clearance; rate of ceramide production; rate of lyso-SPM production; rate of transit of ceramide; Rate of transit of lyso-SPM; rate of SM exchange; rate of export of ceramide into plasma; rate of export of lyso-SPM into plasma; rate of clearance of lyso-SPM from plasma; parameters controlling lyso-SPM export; maximum SM amount in hepatocytes/macrophages in ASMD; parameters controlling macrophage function in lung/spleen;) **Spleen** sub-model parameters (i.e., Rates controlling spleen sub-volumes; maximum spleen volume) **Lung** sub-model parameters (i.e., Rates controlling Hb-adjusted percent predicted DLco; maximum and minimum Hb-adjusted percent predictd DLco)
Development/ Refinement/ Validation	DFI13803	**Phase 1/2** clinical trials (Pediatric ASMD patients, Intrapatient dose escalation 0.03 - 0.1 - 0.3 - 0.3 - 0.6 - 1.0 - 2.0 - 3.0 (target) mg/kg, Q2W, 64 weeks)	**Spleen** sub-model parameters (i.e., Rates controlling spleen sub-volumes; maximum spleen volume) **Lung** sub-model parameters (i.e., Rates controlling Hb-adjusted percent predicted DLco; maximum and minimum Hb-adjusted percent predictd DLco)
Development/ Refinement	LTS13632	**Phase 2** clinical trials (ASMD adult and pediatric patients rolled over from DFI13412 and DFI13803, 9 years or marketing approval)	**Spleen** sub-model parameters (i.e., Rates controlling spleen sub-volumes; maximum spleen volume) **Lung** sub-model parameters (i.e., Maximum Hb-adjusted percent predictd DLco)
Development/ Validation/ Refinement	DFI12712	**Phase 2/3** clinical trials (Adult ASMD patients, Intrapatient dose escalation 0.1- 0.3- 0.3- 0.6- 0.6- 1.0- 2.0-3.0 -3.0 (target) mg/kg, Q2W, in total (PAP + ETP), the trial will last for to up to 5 years and 3 months))	**Spleen** sub-model parameters (i.e., Maximum spleen volume) **Lung** sub-model parameters (i.e., Maximum and minimum Hb-adjusted percent predictd DLco)

From www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf

Reviewer conducted extensive review to verify:

- ***Data quality***
- ***More ..***

Parameter and Assumption Check

Fixed parameters: values directly from literature or nonclinical studies

Estimated parameters: values estimated based on literature, preclinical and clinical data

Calibrated parameters: values allowed to vary and calibrated based on clinical data

- Parameter Check is conducted based on various sources.

- Model Assumptions and biological plausibility should be assessed.

Assumptions on biological process, including disease progression, scaling, and pharmacological effect.

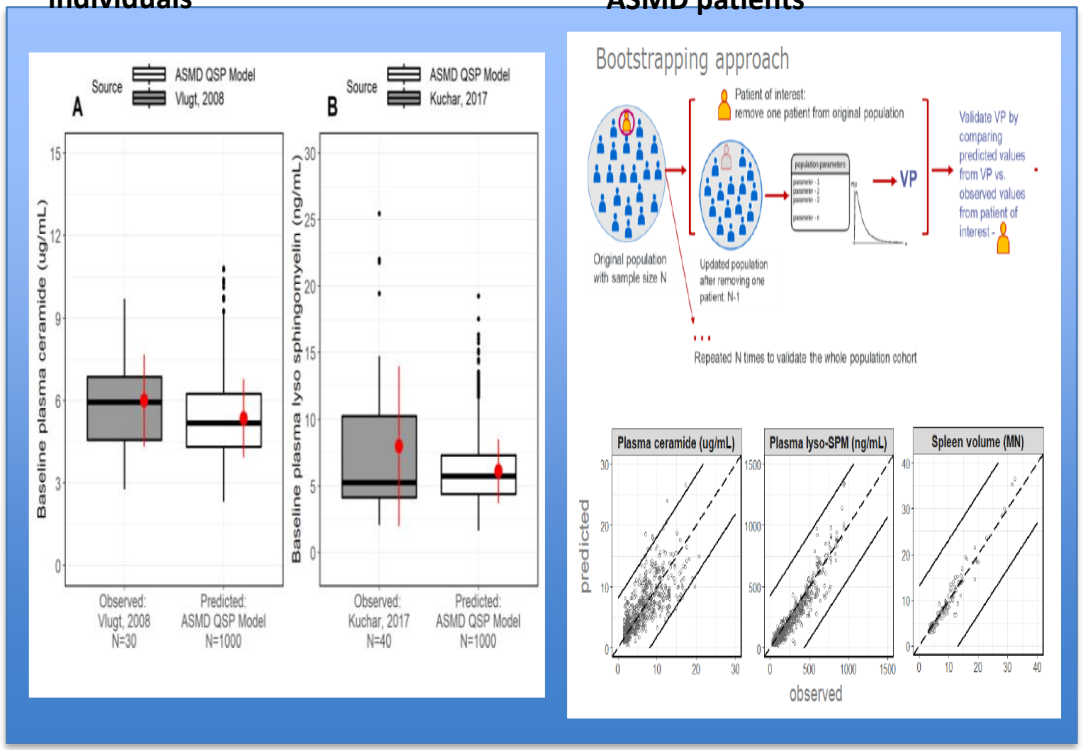
Assumptions on mathematics, including underlying model structure, and parameter distribution.

Model Evaluation & Similarity Comparison

Model Validation

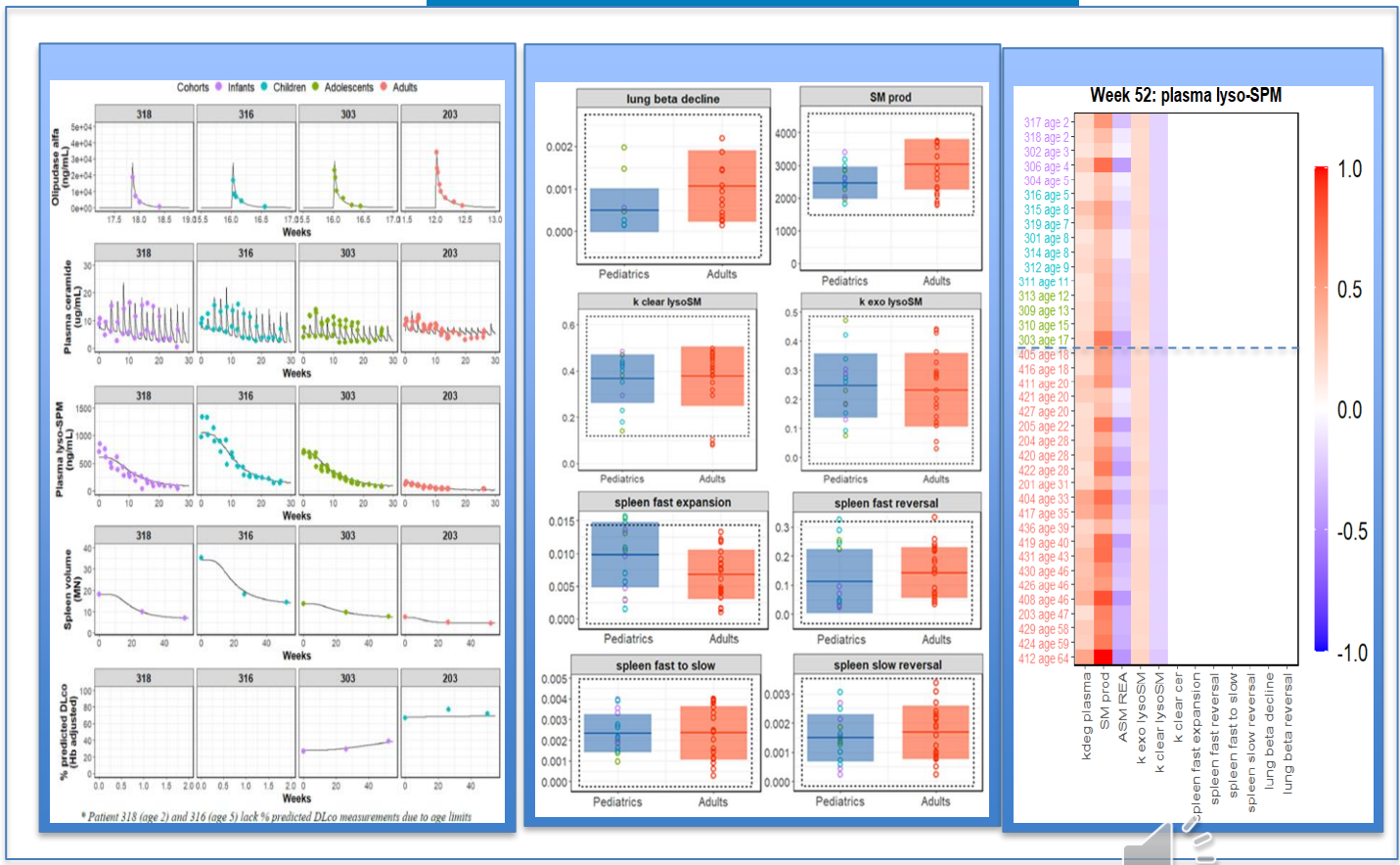
Virtual population of healthy individuals

Virtual population of pediatric ASMD patients



Virtual population shows good agreement with validation dataset, as biomarkers and clinical endpoints both show similar trends with considerable amount overlap in their variability ranges.

Similarity Comparison



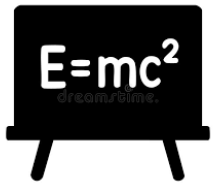
Individual Fitting

Parameter Comparison

Sensitivity Analysis

Challenges for Assessing Mechanistic Models 1

- Mechanistic basis:
  - Current/evolving understanding, and knowledge of the mechanism
  - Competing/alternative biological theories
  - Rationale for the selected mechanism as the basis for model building

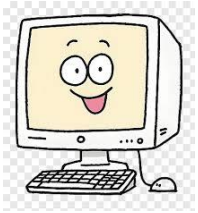


- Parameter sources:
  - Solid study design, reliable study conduct for parameter generation
  - Relevance of *in vitro* or animal findings
  - Relevance of parameters derived from healthy subjects or patients with different diseases
  - Selected values from a broad range / variability of reported values

- Scaling and/or translational findings:
  - Scaling that reflects microenvironment and heterogenous distribution (e.g., of enzyme and receptors)
  - Translation of non-clinical findings

Challenges for Assessing Mechanistic Models 2

- Model calibration
  - Appropriate data source
  - Selection of parameters for calibration
  - Sensitivity to model performance



- Software / platform / code verification
  - Suitability of the algorithm
  - Robustness for handling complicated data and scenarios
  - Extreme scenarios when “bugs” occur.

- Model Validation
  - External validation
  - Repeated validation with new clinical trial data.

Opportunities for Collaboration

- Multidisciplinary inputs are critical for mechanistic model evaluation.
  - Biologists, pharmacologists, medical professionals, data scientists, software engineers, pharmacometricians
- Effective communication among tool developers, sponsors, and regulatory agency is essential.
  - Mechanistic model development becomes a continuous process over years or decades. Communication often occurs as “snapshots” during model development for a specific phase of drug development.
  - Review timelines are relatively short.
- Collaborative effort across stake holders (e.g., academia, industry, and agency) provides the foundation for innovation.
  - Adoption of the latest development in mechanistic understanding.
  - Inclusion of the new dataset and trial for model building or validation.
  - Application of novel tools that can be applied for model development.
  - Building trust and ensuring transparency.

Take Home Messages

- Mechanistic modeling is playing increasingly important roles in new drug development.
- Both PBPK modeling and QSP modeling, two common mechanistic modeling approaches, are playing important roles in submissions and reviews at the US FDA.
  - As reflected in the review of Olipudase Alpha, a risk-based, comprehensive approach has been taken to assess the model performance.
- Assessing mechanistic modeling is still technically challenging, yet full of opportunities for collaboration.
  - Multidisciplinary inputs, effective communication, trust-building, and collective efforts across all stake holders are critical.
  - Future collaboration in the scientific community is necessary to improve the potential use of mechanistic modeling for evidence generation and decision-making.

Acknowledgement

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- CBER colleagues