Utility of the Advanced Oral Absorption Modeling in Clinical Pharmacology Assessment

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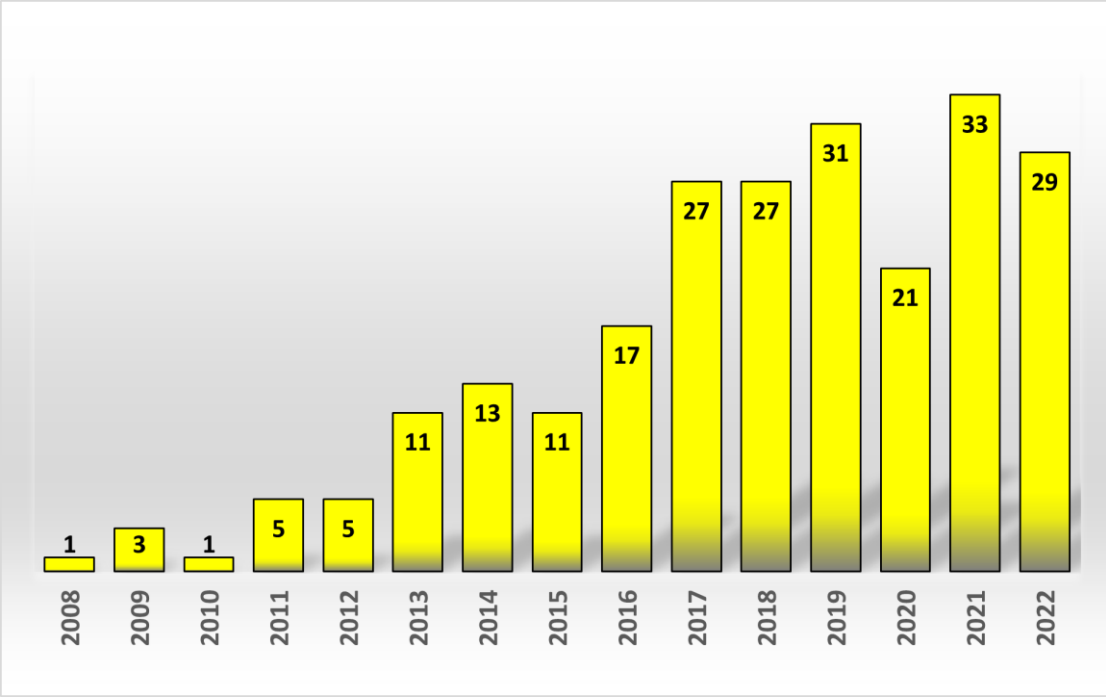
- The views expressed in this presentation are that of the speakers and do not reflect the official policy of the FDA.
- Cases discussed are for illustrative purpose only. No official endorsement by the FDA is intended nor should be inferred.

Outline

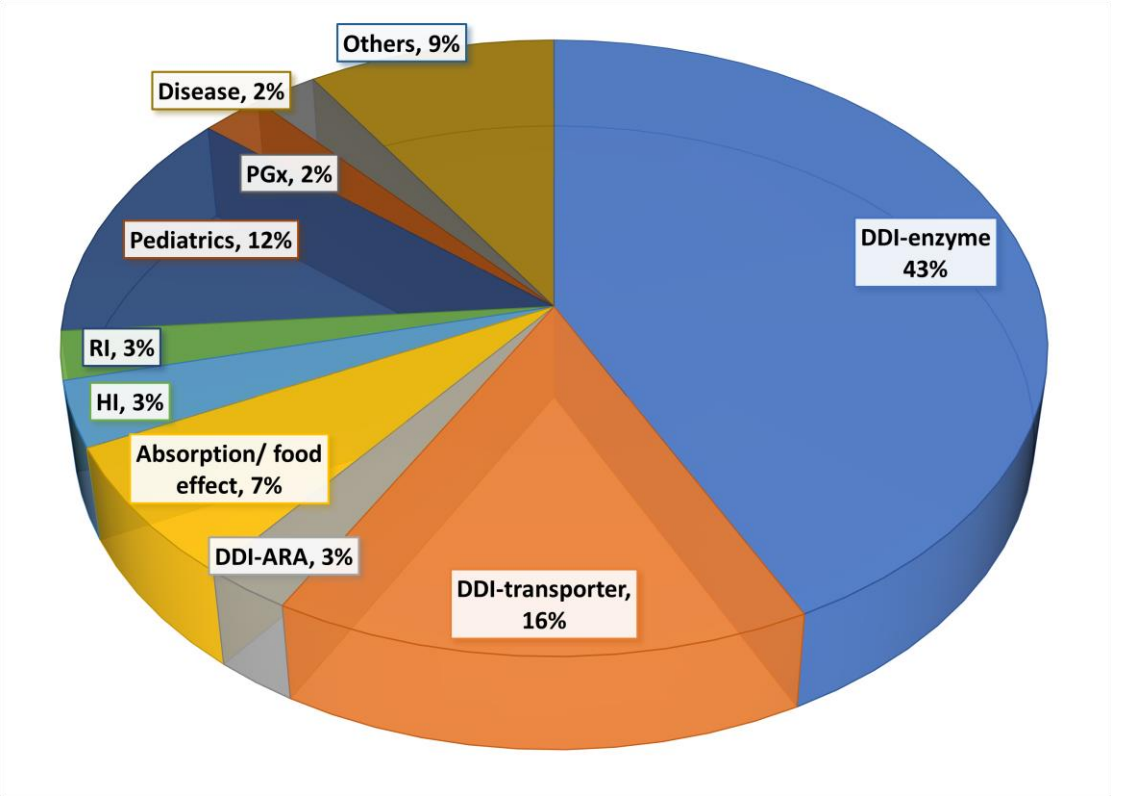
- Current PBPK Status in New Drug Development and Regulatory Assessment
  - Recent PBPK Submissions to Office of Clinical Pharmacology
- Advanced Absorption Modeling for Clinical Pharmacology Assessment
  - Current and Potential Application Areas
  - Case Examples
- Summary

PBPK in Clinical Pharmacology Assessment

Number of NDA submissions containing PBPK analyses (2008 - 2022)

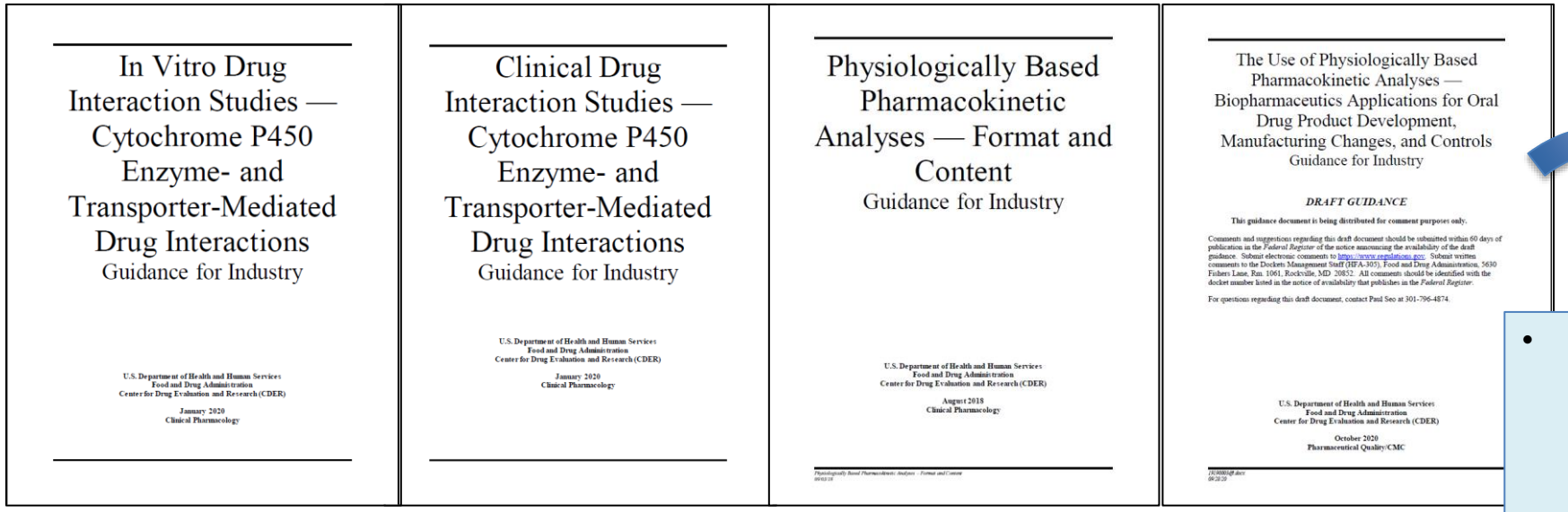


Areas of Application in IND/NDA/BLA N=368, NDA=137 (2018- 2022)



Slide Courtesy of Dr. Manuela Grimstein. Updated the previously published information (Grimstein et al. J Pharm Sci. 2019 Jan;108(1):21-25 and Zhang et al., J Clin Pharmacol. 2020 Oct;60 Suppl1:S160-S178.)

PBPK related Guidances



- *How to develop and evaluate PBPK models for biopharmaceutics applications for oral drug products (IND/NDA/ANDA)*
- *Focused on drug product quality and a mechanistic understanding of their interaction with physiology to affect in vivo drug performance*

PBPK is also in:

- Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications (March 2023)
- General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (September 2022)
- Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations (June 2022)
- M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Draft Version, December 2022)

FDA encourages sponsors to contact FDA regarding their PBPK modeling and simulation plan.

Leveraging Advanced Absorption Modeling for Clinical Pharmacology Assessment

- Mechanistically characterize complex oral absorption matters arising from the interplay of drug physicochemical properties - formulation characteristics - physiological factors

  - Elevated gastric pH (e.g., pH-dependent DDIs)
  - GI condition changes (e.g., delayed emptying time)
  - Specific populations (e.g., pediatrics, geriatrics)
  - GI enzymes/transporters mediated DDIs (e.g., P-gp mediated DDIs)
  - Food effects
  - Formulation/delivery mechanism differences (e.g., pediatric formulation)
  - Excipient effects (e.g., DDI due to excipients in coadministered drug)

Case Examples

- pH-dependent DDIs with ARAs
  - Duvelisib
  - Asciminib
- Pediatric PK
  - Entrectinib
  - Rivaroxaban
- Excipient interaction
  - Cyclodextrin*

** This case is based on the published information in Durk et al., 2020 (doi:10.1002/cpt.1943). No official endorsement by the FDA is intended nor should be inferred.*

Case #1 – Duvelisib
Background and PBPK Objective

- Duvelisib solubility is pH dependent and decreases with increasing pH
- Increased gastric pH due to acid reducing agents (ARAs) may lower the solubility and thus exposure
- Drug particle size can affect dissolution and drug exposure of duvelisib
- The applicant submitted PBPK model for biopharmaceutical and clinical pharmacology applications
  - The model was acceptable to support drug substance particle size distribution (PSD) specification for duvelisib capsules
- The goal of this PBPK modeling analysis was to evaluate duvelisib pH-DDI potential with ARAs while accounting for drug particle size effects on dissolution

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000ChemR.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf

Duvelisib PBPK Absorption Model Development, Validation and Application

Model Development

- **Key input parameters for absorption model**
  - **Solubility at different pH (buffer & biorelevant media)**
  - **Precipitation time** fitted to PK data – supported by supersaturation status in solution at 0.1 & 0.3 mg/ml remained for up to 24 hr in FaSSIF (pH 6.5) and FeSSIF (pH 5.0)
  - **Drug particle size distribution**
  - **Gastric pH & Gastric emptying time**
- Model adequately described the observed PK (AUC and Cmax) with varying doses and formulations of duvelisib

Model Validation

- Model captured the observed duvelisib PK for a wide range of doses and PSDs
- **Model performance was considered acceptable** for assessing elevated gastric pH effects on duvelisib PK

Model Application

Evaluation of clinical significance of duvelisib PK change due to pH-dependent DDI with ARAs

- **PBPK simulation to assess elevated gastric pH effects on duvelisib exposure**
- **Parameter sensitivity analysis on Fabs**
  - Particle size distribution
  - Dose
  - Gastric pH

- **In vitro** measured & ADMET predictor (solubility in multiple pH buffers & SGF, FaSSIF media; pKa)
- **Particle Size Distribution** for different batches

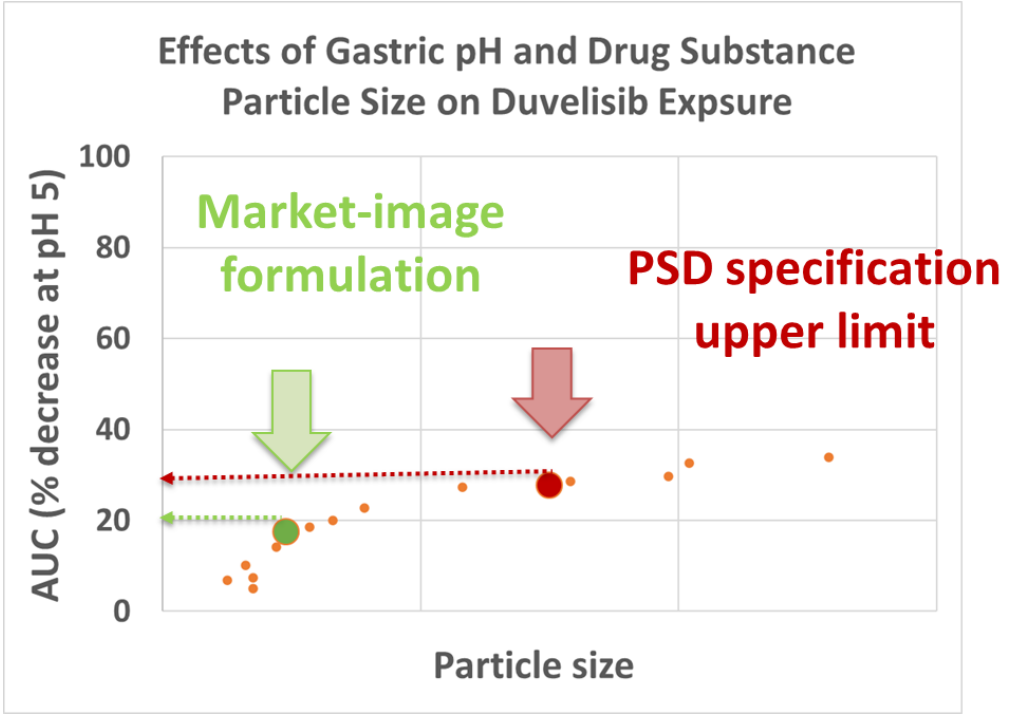
- IV PK study & **Clinical studies** (9 for development ad 5 for validation) with
  - a **wide dose** range (1-30 mg)
  - unique **PSDs** not used in model development including those beyond the agreed specification

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000ChemR.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf

Predicting pH DDI Potential and Risk Assessment

- The effect of elevated gastric pH on duvelisib PK increases with increasing drug substance particle size distribution following a single dose of 25 mg
- When stomach pH was increased to 5 compared to pH 1.3, duvelisib exposure was decreased by
  - **Market-image formulation:** 17% and 65% in AUC and Cmax, respectively
  - **At PSD specification upper limit**: 28% and 66% in AUC and Cmax, respectively
- **Overall, the predicted effect was considered not clinically meaningful**



Note: Duvelisib AUC and D50 are plotted for the illustration purpose using the data extracted from Table 123 in the multi-discipline review/summary, clinical, non-clinical (refer to the link). For full details of the simulation, refer to the FDA review linked below. Duvelisib oral capsules recommended dosing is 25 mg BID with or without food in the label.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf

Duvelisib Case Summary

- The applicant's absorption PBPK model was acceptable for the proposed purpose
  - Assessed the impact of elevated gastric pH on duvelisib PK while accounting for the effect of drug particle size
  - Risk assessment via sensitivity analyses by the applicant and FDA reviewer for pH DDI potential evaluation close to the upper bound of particle size distribution specification
- The absorption PBPK analysis supported regulatory decision that the drug product can be administered with acid reducing agents

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf

Case #2 Asciminib
Background and PBPK Objective

- Asciminib exhibits pH-dependent solubility decreases with increasing pH
- Clinical DDI study with rabeprazole (proton pump inhibitor) and asciminib 40 mg did not show clinically meaningful pH DDI effect
- In response to the FDA's information request to address the effect of elevated gastric pH on asciminib PK at a higher dose of 200 mg, the applicant submitted two-stage in vitro dissolution and PBPK modeling
- The goal of the PBPK modeling was to evaluate the impact of asciminib dose on the magnitude of asciminib PK change by elevated gastric pH

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215358Orig1s000,Orig2s000MultidisciplineR.pdf

Asciminib PBPK Absorption Model Development, Validation and Application

Model Development

- **Key input parameters for absorption model**
  - **Solubility & pKa**
  - **Particle size**
  - **Bile salt micelles:water partition coefficient (logKm:w)**
  - **Supersaturation & Precipitation**

- Analysis of the in vitro data to estimate parameters
  - In vitro solubility data (aqueous buffer in different pH and biorelevant media FaSSIF)
  - In vitro two-stage dissolution data (biorelevant conditions of normal vs. hypochlohydric)

- Updated the originally developed PBPK model for DDI evaluation

Model Validation

- Model adequately captured the observed PK following a range of single and multiple dose of asciminib
- In vitro to in vivo extrapolation of dissolution and solubility data for asciminib was inferred as reasonable

- Sensitivity analysis *
  - Particle size
  - Bile salt micells:water PC
  - Critical supersaturation ratio

- Clinical PK studies in healthy subjects and patients (40 – 200 mg dose range) and the clinical rabeprazole DDI study

Model Application

Evaluation of clinical significance of asciminib PK change due to pH DDI effect with ARAs + in vitro dissolution data + clinical DDI study with rabeprazole and 40 mg asciminib

- **PBPK simulations to assess the magnitude of elevated gastric pH effect on asciminib PK after 40 mg vs. 200 mg**
- **Conservative simulation condition** (DDI potential more sensitive to changes in bile salt PC and CSR at higher dose)

** Applicant's response to FDA IR and FDA reviewer's own analysis*

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215358Orig1s000,Orig2s000MultidisciplineR.pdf

PBPK Addressed pH DDI Potential of Asciminib at a Higher Dose & Provided Mechanistic Explanation

	Trial	Elevated Gastric pH Effect (Ratio)	
		Cmax	AUC
Asciminib (40 mg) + Rabeprazole	Observed	0.908	0.986
Asciminib (40 mg) + Rabeprazole	Simulated	0.994	1.00
Asciminib (200 mg) + Rabeprazole	**Simulated***	**0.72**	**0.77**

Note: Summarized the data extracted from the Table 57 and the multi-discipline review (refer to the link). * FDA reviewer's sensitivity analysis.

- The PBPK analysis results suggested that changes in gastric pH does not have much effect on asciminib exposure *"due to its high solubility in bile salts attributed to supersaturation, which override the pH effect"*

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215358Orig1s000,Orig2s000MultidisciplineR.pdf

Asciminib Case Summary

- The applicant's absorption PBPK model was adequate for the purpose of evaluation of the effect of elevated gastric pH on asciminib exposure at a higher dose (200 mg)

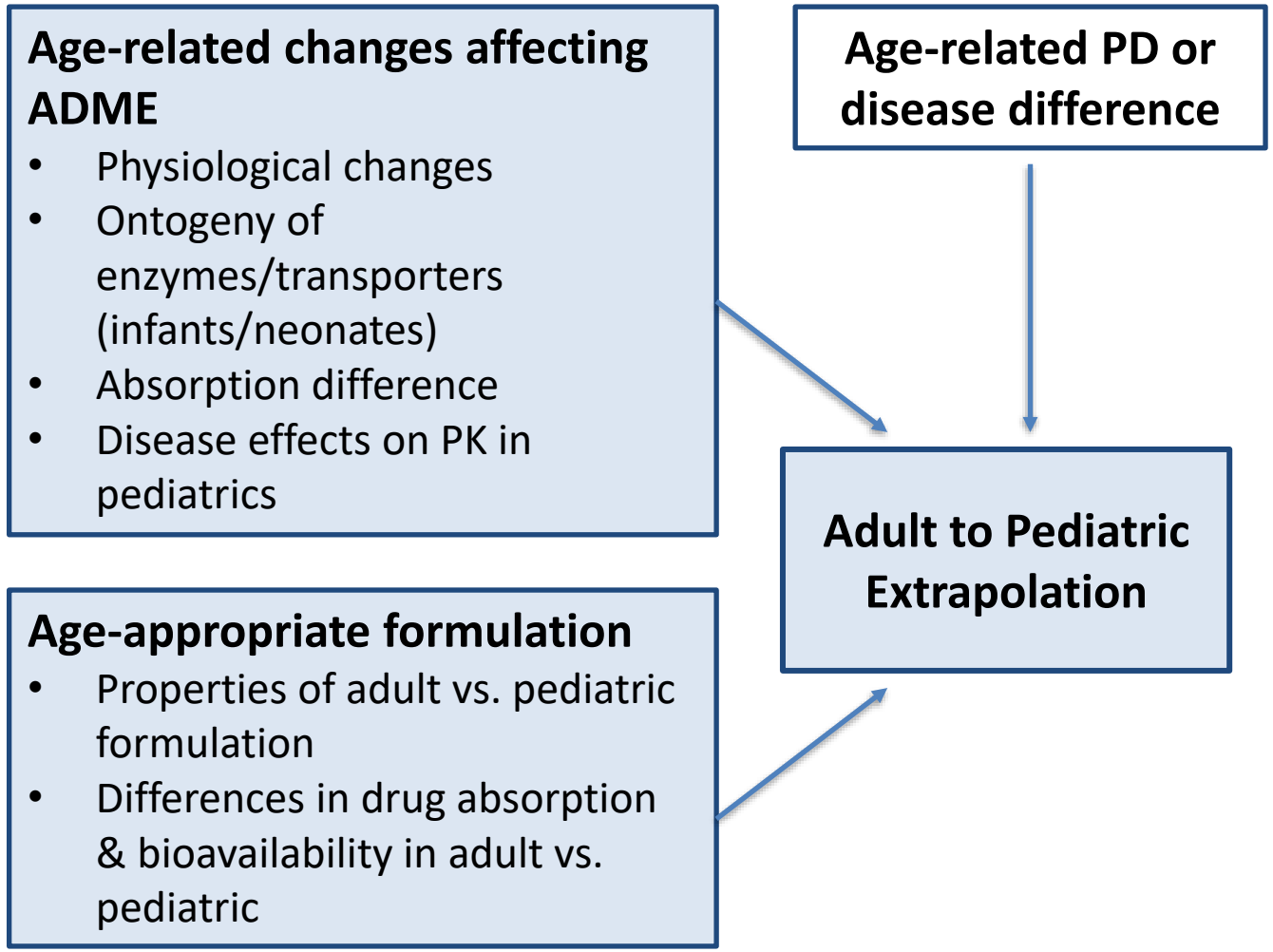
- Regulatory decision was supported by this PBPK analysis, the in vitro dissolution data and clinical DDI study with rabeprazole at a lower dose of asciminib (40 mg)

- The PBPK analysis provided support to the labeling *"No clinically significant differences in the pharmacokinetics of asciminib were observed when coadministered with rabeprazole (acid-reducing agent)…"*

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215358s000Orig2lbl.pdf

PBPK in Support of Pediatric Drug Development Program

- PBPK has been used to support initial dose selection for pediatric trials
- PBPK can support pediatric formulation development
  - Mechanistically accounting for age-related absorption differences
  - Bridging the observed relative BA and BE in adults to pediatrics



Case #3 Entrectinib
Background and PBPK Objective

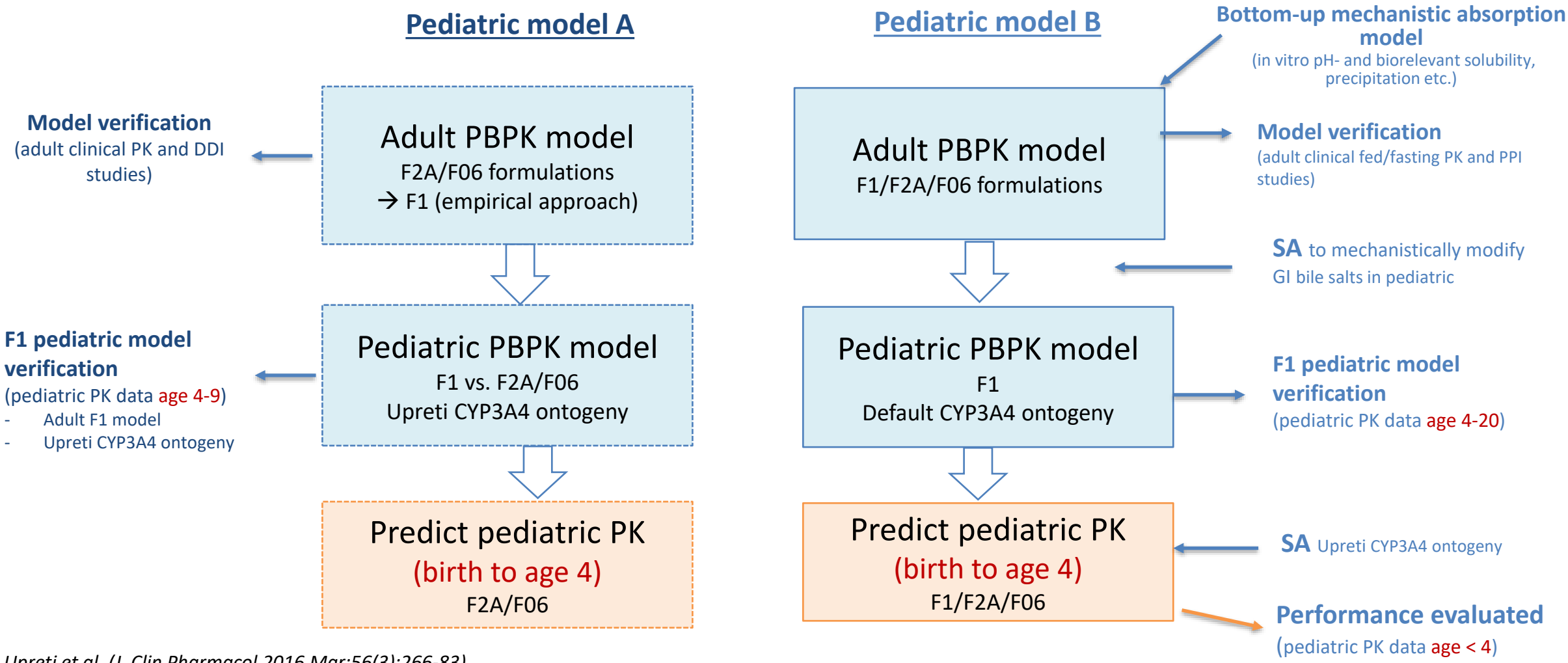
- Entrectinib has low and pH-dependent solubility, moderate permeability in vitro and is cleared largely through metabolism (CYP3A4)

- Multiple formulations were developed at various stages of the drug development program
  - F1 showed pH-dependent DDI effect with a proton pump inhibitor lansoprazole
  - F2A (pivotal clinical formulation) and F06 (to-be-marketed formulation) included acidulant to reduce the pH-dependent DDI effect
  - F2A and F06 were shown bioequivalent in adults
  - In the pediatric clinical studies, only F1 was used

- The applicant proposed to use PBPK modeling to predict entrectinib PK in pediatric population (birth to 4 years) following administration of F1/F2A/F06 formulations

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%20212726Orig1s000MultidisciplineR.pdf

Applicant's Pediatric PBPK Modeling Workflow



Upreti et al. (J. Clin Pharmacol.2016 Mar;56(3):266-83)
Applicant's workflow is illustrated based on the FDA published review available at
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%20212726Orig1s000MultidisciplineR.pdf

Entrectinib Case Summary

- FDA concluded that the applicant's pediatric PBPK models were both not acceptable for the purpose of predicting entrectinib PK in pediatric subjects less than 4 years of age
- Some highlights of the gaps
  - Absorption not modeled mechanistically, which could not fully and mechanistically capture the impact of GI physiology change on PK and difficult to extrapolate
  - Formulation difference was empirically modeled by adjusting permeability, which was not supported by evidence
  - Tendency to overestimate pediatric exposure in less than age 4, even with alternative Upreti ontogeny
- Highlighted the current challenges/uncertainties in modeling pediatric absorption and CYP3A ontogeny
  - Ontogeny profiles have significant impacts on entrectinib PK profiles across ages, while it was still not adequately explaining the discrepancy

Zhang et al., J Clin Pharmacol. 2020 Oct;60 Suppl1:S160-S178
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%20212726Orig1s000MultidisciplineR.pdf

Case #4 – Rivaroxaban
Background and PBPK Objective

- Modeling and simulation were applied through out the rivaroxaban pediatric development program, including support dose selection for pediatric trials in early phases of the program
- Age-appropriate formulation (granules for oral suspension) was BE to the adult formulation (IR tablet) in adults, but shown delayed absorption in younger children (age 6-12)
- This case shows how PBPK modeling was used to support use of pediatric formulation

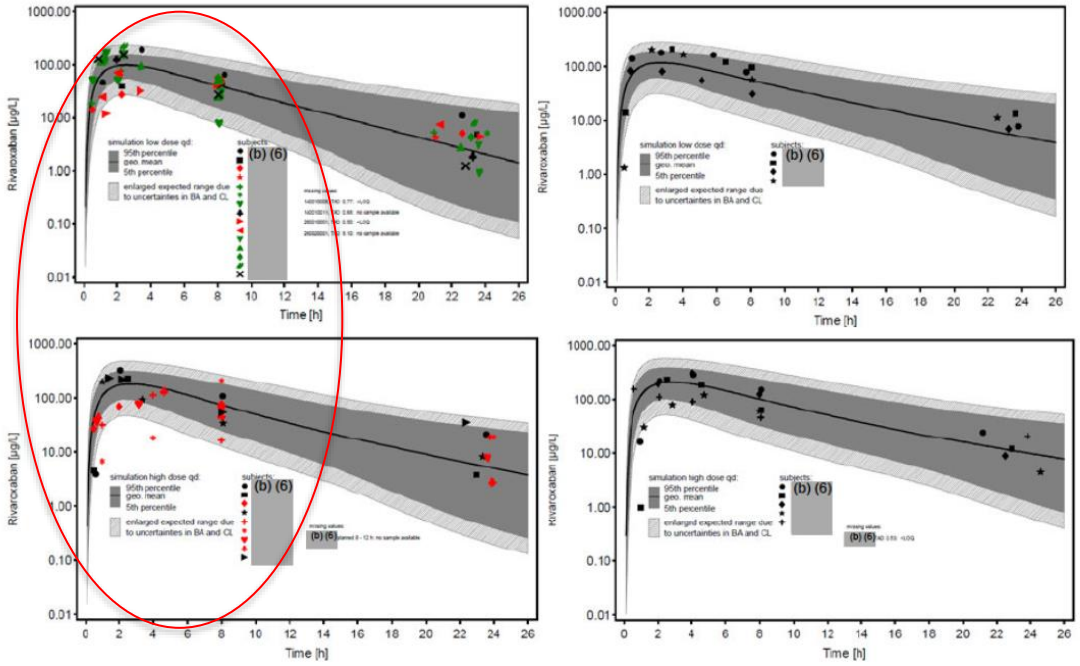
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215859Orig1s000ClinPharmR.pdf

PBPK Provided Mechanistic Explanation for Delayed Absorption with Age-Appropriate Formulation

Comparison of Predicted vs. Observed Rivaroxaban PK Profiles

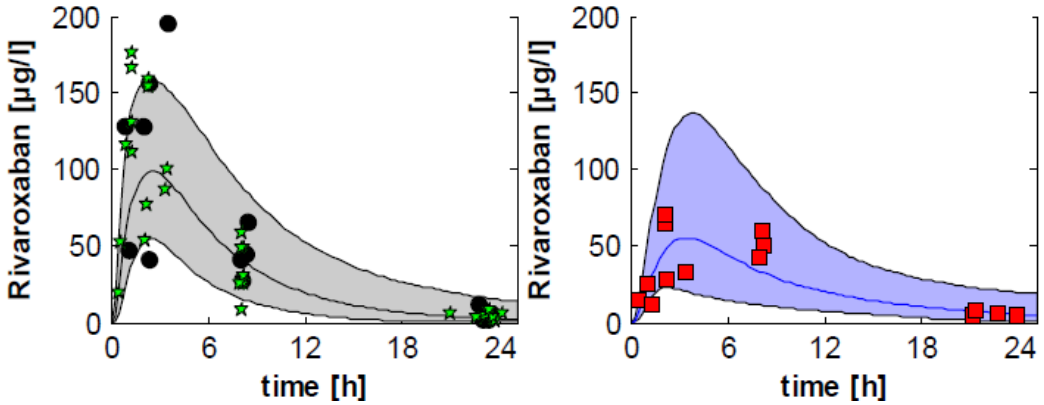
A. Different Age Groups

Age 6 - <12 years ***Age 12 - <18 years***



B. Different Formulations in Age 6-12 Years

Default Dissolution Rate ***Reduced Dissolution Rate***



● **Tablet,** ▪ **Undiluted suspension,** * **Diluted Suspension**

Source: Plots are extracted from Figures 52 & 57 from the clinical pharmacology review(s) available at the link.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215859Orig1s000ClinPharmR.pdf

Rivaroxaban Case Summary

- PBPK analysis supported mechanistic explanation for the observed delayed absorption of rivaroxaban in younger children (age 6-12) received undiluted suspension formulation
  - Absorption model described the rivaroxaban PK difference from diluted vs. undiluted suspension formulations in pediatric subjects using the dissolution rate difference
- Consequently, BW adjusted dose of the diluted ready-to-use suspension (pediatric formulation) was used in subsequent pediatric trials

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215859Orig1s000ClinPharmR.pdf

Excipient-Drug Interactions

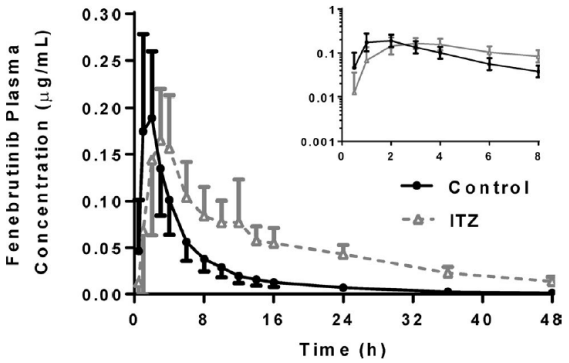
- Absorption PBPK modeling may be useful to support in assessing excipient-drug interaction potential

- A recently published fenebrutinib DDI study* with itraconazole in solution is discussed to illustrate the potential opportunity in this area

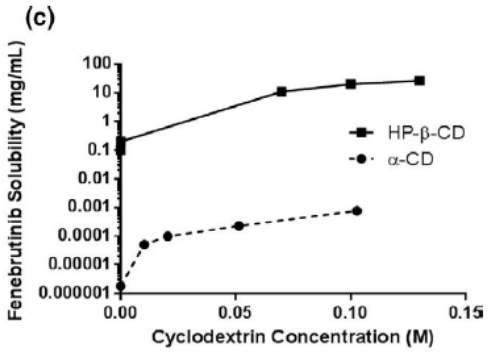
  – In the published study*, a retrospective PBPK analysis was used to mechanistically explain the confounded DDI based on the interaction between fenebrutinib and hydroxypropyl-β-cyclodextrin in itraconazole oral solution, along with in vitro studies

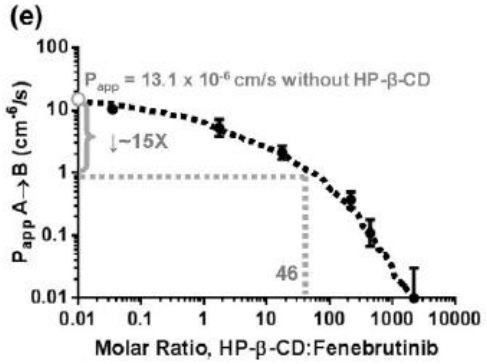
** The discussed case is based on information from Durk et al., 2020 (doi:10.1002/cpt.1943) publication. No official endorsement by the FDA is intended nor should be inferred.*

*Case #5 Cyclodextrin Effect as Excipient on Fenebrutinib PK

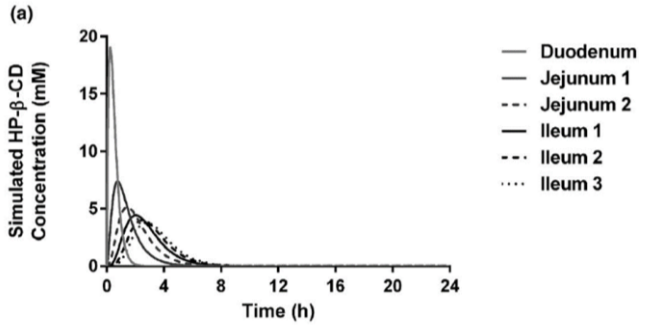


Fenebrutinib-itraconazole DDI was observed not as expected

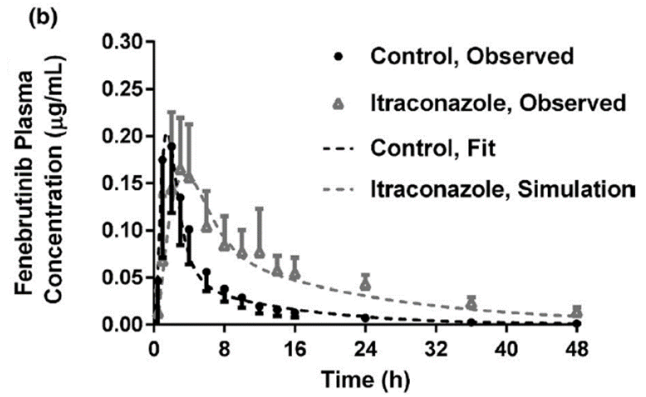




In vitro data supported the hypothesis of fenebrutinib forming a strong complex with HP-β-CD → solubility ↑, Papp↓ in vitro



PBPK simulated GI profiles of HP- β -CD used to adjust fenebrutinib permeability in the model



PBPK model captured the observed HP- β -CD effect (as itraconazole coadministration) on fenebrutinib PK

** The discussed case is based on information from Durk et al., 2020 (doi:10.1002/cpt.1943) from which the plots were extracted from Figures 2 and 3.*

Cyclodextrin Excipient Case summary

- In this published study*, absorption PBPK modeling retrospectively provided mechanistic explanation to the observed confounded DDI due to the contribution of the excipient in the coadministered drug

- Mechanistic absorption modeling may be used to support addressing drug-excipient interactions that may arise for other drugs/excipients

** The discussed case is based on information from Durk et al., 2020 (doi:10.1002/cpt.1943) publication. No official endorsement by the FDA is intended nor should be inferred.*

Overall Summary

- Regulatory experience is being built in the application of PBPK advanced absorption models to clinical pharmacology assessment
- Current application examples were shared to provide insights into the potential opportunities and areas for further improvement
- To increase confidence, continued efforts are needed to further demonstrate/improve the following areas
  - The ability to prospectively predict the effects of drug product formulation on in vivo drug PK
  - The in vitro to in vivo extrapolation of key absorption related parameters
  - The understanding of age-related changes in GI absorption physiology (esp. <age 2) and the impacts on interactions with drug and/or formulation properties during absorption

Acknowledgement

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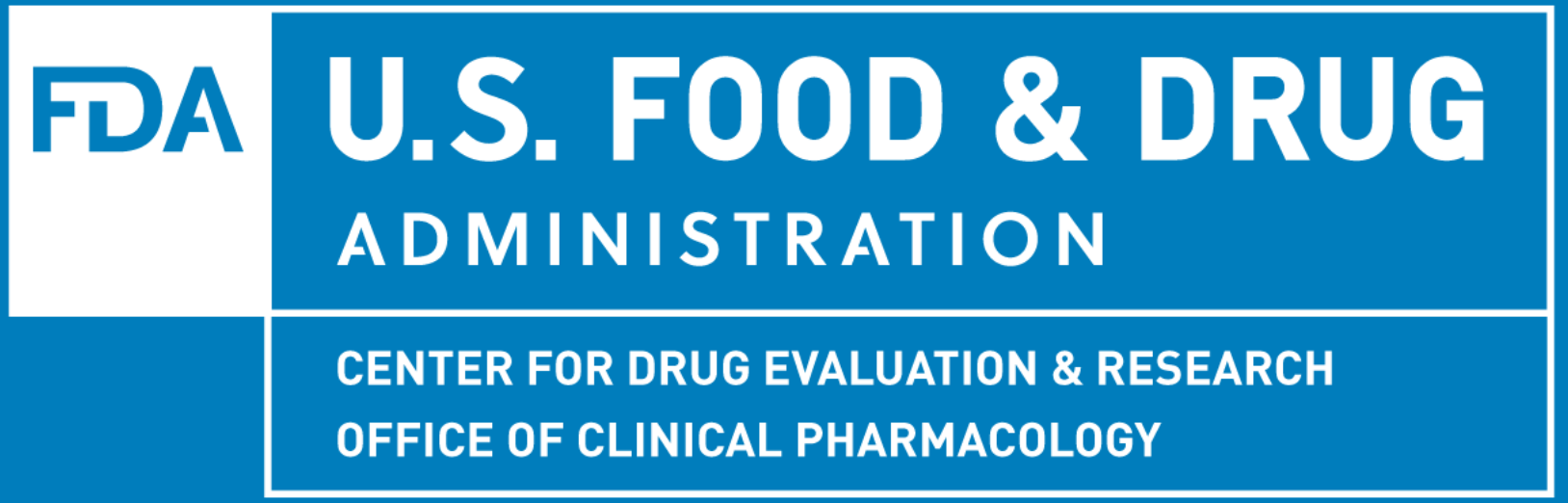
- OCP and DPM colleagues
- OCP DPM: Drs. Hao Zhu and Jiang Liu
- OCP IO: Office Leadership
- Applicants and review teams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