Application of PBPK Modeling in Regulatory Submission: FDA Experience on Generic Drugs

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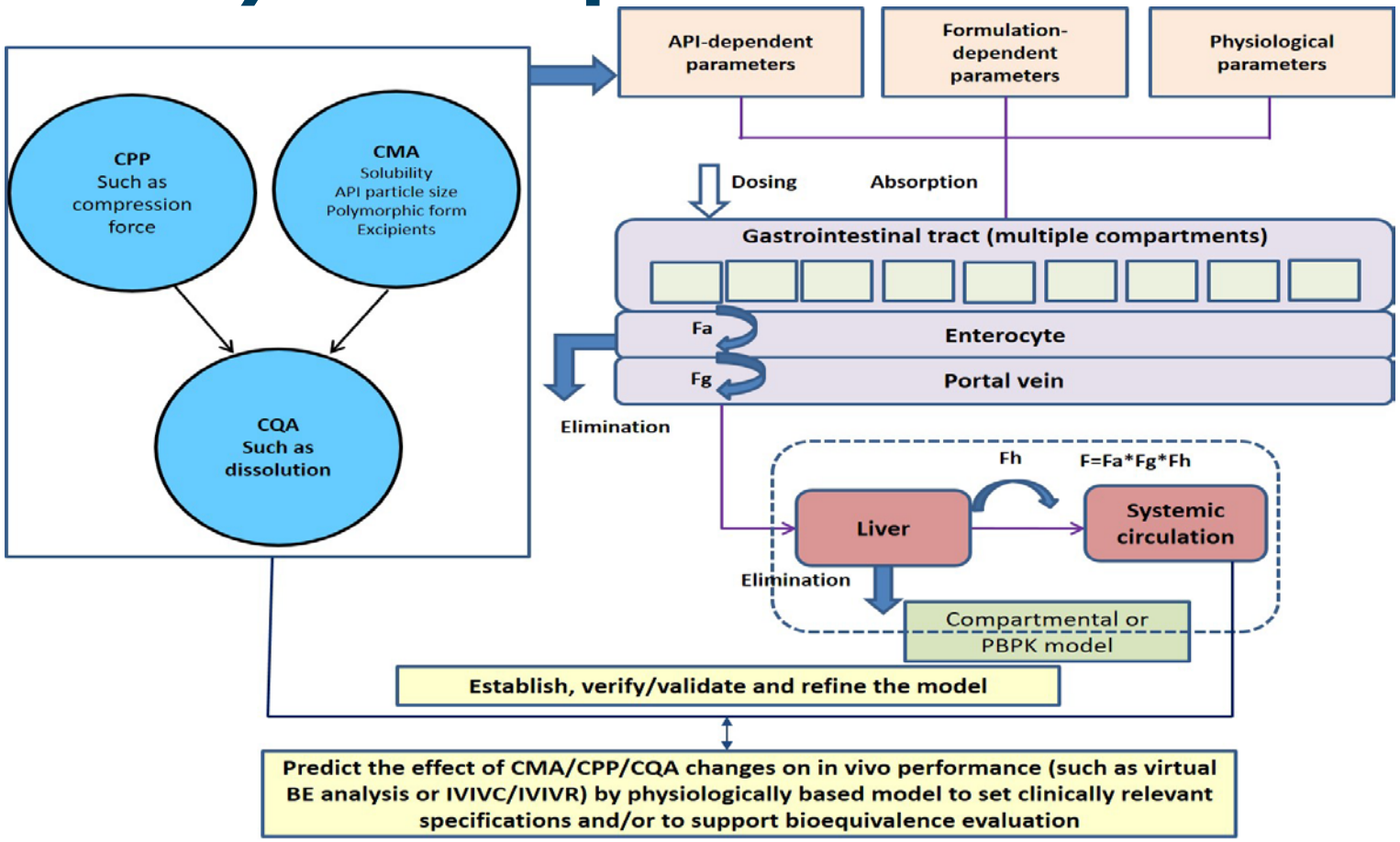
Outline of the Presentation

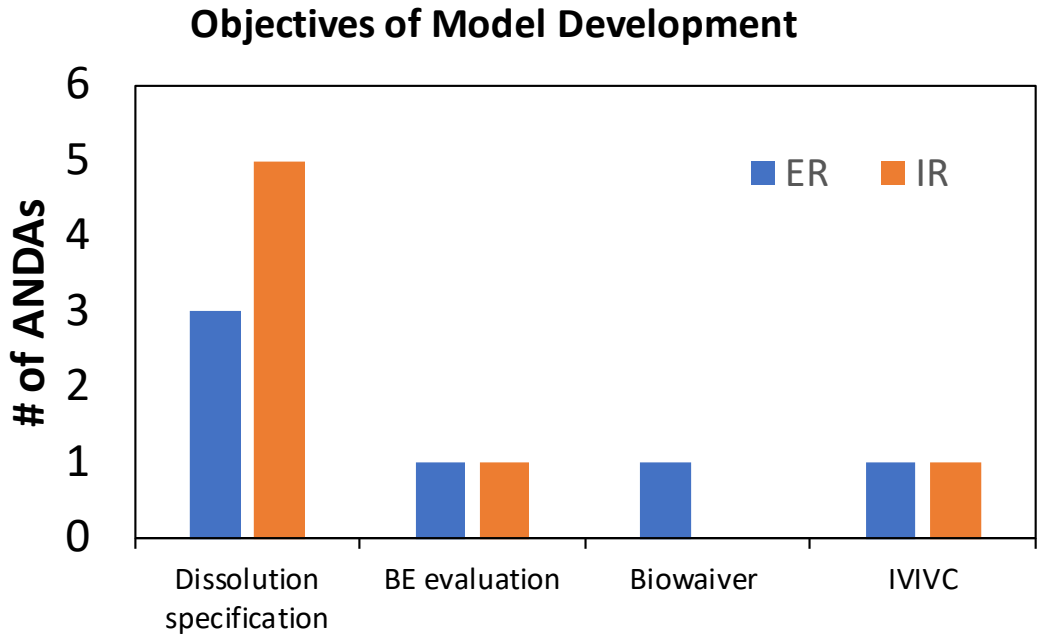
1. PBPK Absorption Model and its Applications
2. Types of Questions that PBPK Absorption Model can Inform for Generic Drugs
3. Highlights of PBPK Impacts in Office of Generic Drugs
4. Regulatory Review and Research of the PBPK Absorption Modeling and Simulation Supporting Bioequivalence Evaluation (Case Studies)
5. Challenges and Opportunities

Physiologically Based Pharmacokinetic (PBPK) Absorption Model



CPP: Critical Process Parameters; CMA: Critical Material Attributes; CQA: Critical Quality Attributes; API, Active Pharmaceutical Ingredient; IVIVC/R: In Vitro In Vivo Correlation/Relationship

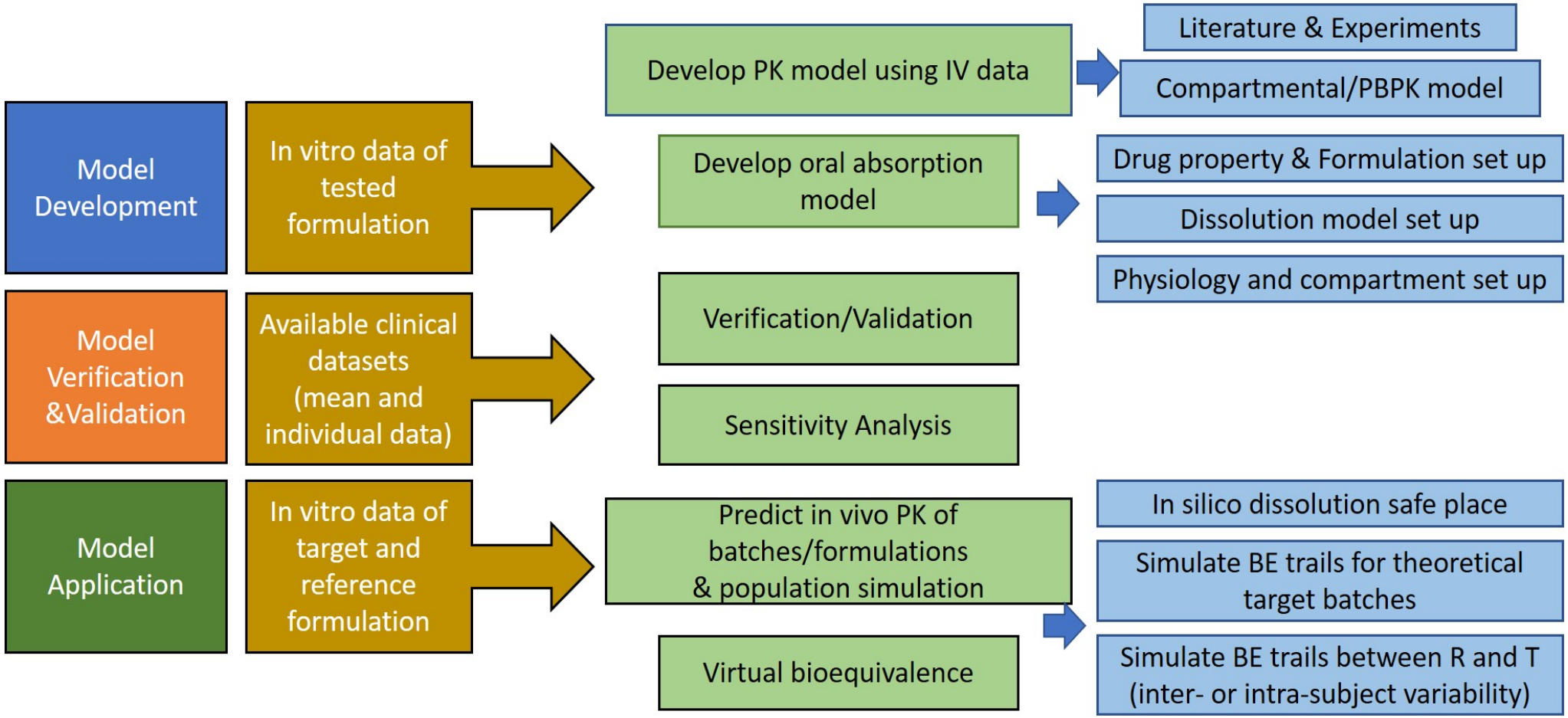
Overview of PBPK Absorption Modeling and Simulation in ANDA Original and Supplement Submissions from 2012-2018



- Major objective is to support dissolution specification settings (8 out of 13 cases from 2012 to 2018)
- Second major objective is to support bioequivalence assessment (2 out of 13 cases)

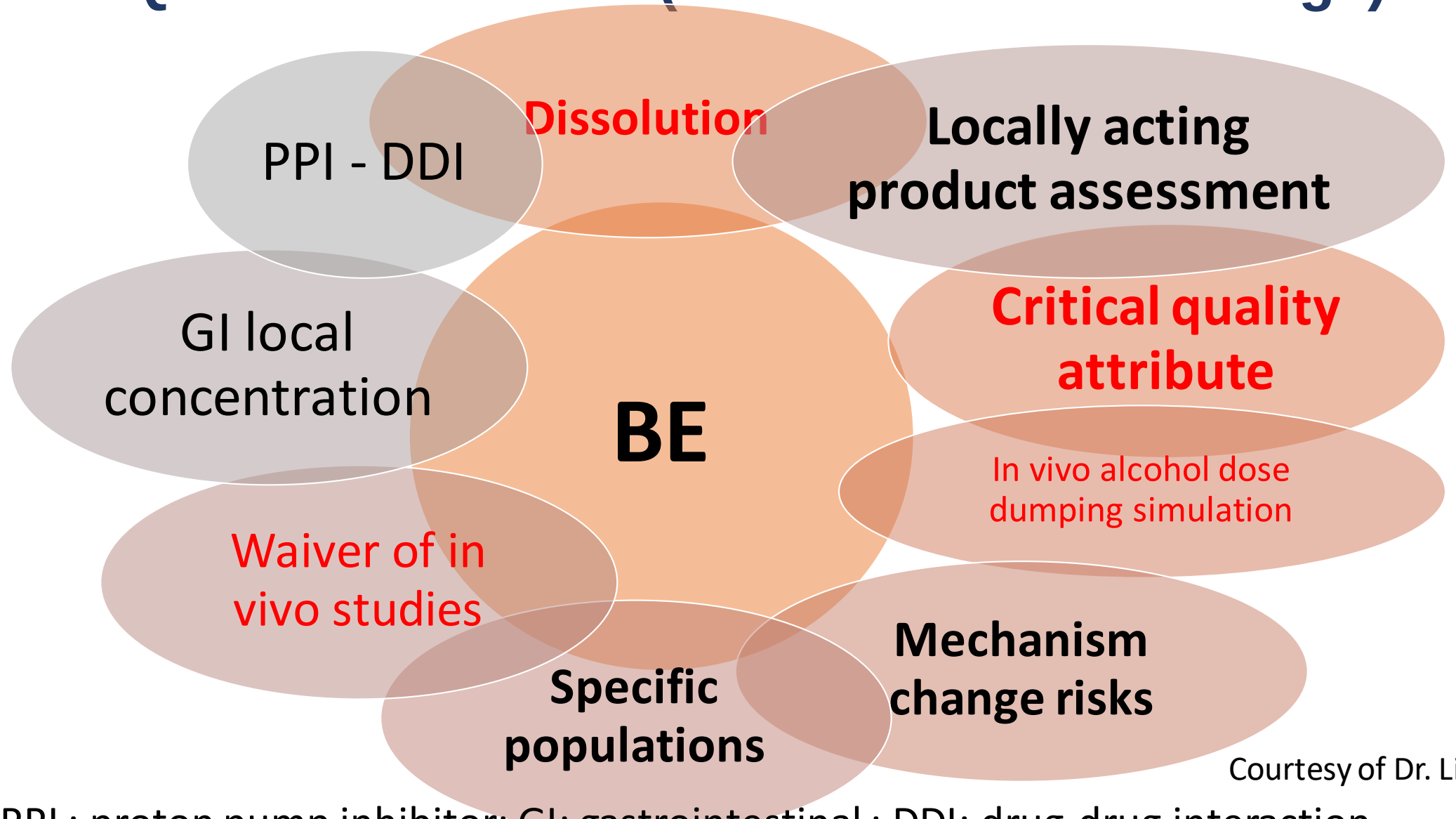
ANDA: Abbreviated New Drug Applications; IR: Immediate Release; ER: Extended Release; BE: Bioequivalence

General Model Procedure in ANDA Submission



PK: pharmacokinetic; IV: intravenous; BE: bioequivalence; T: test product; R: reference product

Types of Questions Models (PBPK for Generic Drugs) Inform



Courtesy of Dr. Liang Zhao

PPI : proton pump inhibitor; GI: gastrointestinal ; DDI: drug-drug interaction

Example: Highlights of PBPK Impacts in OGD

Category	Example Drug	Impact on regulatory decision making
Dissolution	Oxybutynin	Risk assessment for not conducting in vivo studies for lower strength generic products when bioequivalence has been established at higher strengths
Product quality	Prasugrel	Conclusion that less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including subjects on PPI
Mechanism change risks	Venlafaxine	Model predicted that a delayed onset of venlafaxine release up to 4 h predicted to demonstrate BE for the openable matrix release mechanism against the osmotic pump based release mechanism
PPI effect	Several ER products	Risk assessment of changing drug release to a PH dependent mechanism
PK metrics determination	Mesalamine Suppositories	Determination of PK metrics for BE evaluation
Alcohol dose dumping	Metformin Hydrochloride ER Tablet	Assessment of alcohol dose dumping potential
Virtual simulation	Methylphenidate	Assessment of using PBPK model in combination with a two way crossover study to meet the guidance recommendation of a four way crossover study for BE assessment

PPI: proton pump inhibitor; ER : extended release

Courtesy of Dr. Liang Zhao

Case Study: Using a PBPK Absorption to Establish Clinically Relevant Dissolution Safe Space for Oseltamivir in Adult and Pediatric Populations

a. Human Adult PBPK Absorption Model Development & Verification/Validation

- Absorption (OP): described by ACAT™ model
- Distribution and PK (OP and OC): PBPK-Plus™ module
- Dissolution model: use in vitro dissolution data as input
- Physiologies: generated by PEAR™ Physiology module
- Metabolism of OP to OC: liver carboxylesterase 1 (CES1)
- Renal clearance (OC) : filtration & active secretion
- Permeability/Perfusion-limited disposition model for liver and other organs, respectively.

b. Human Pediatric PBPK Absorption Model Extrapolation & Verification/Validation

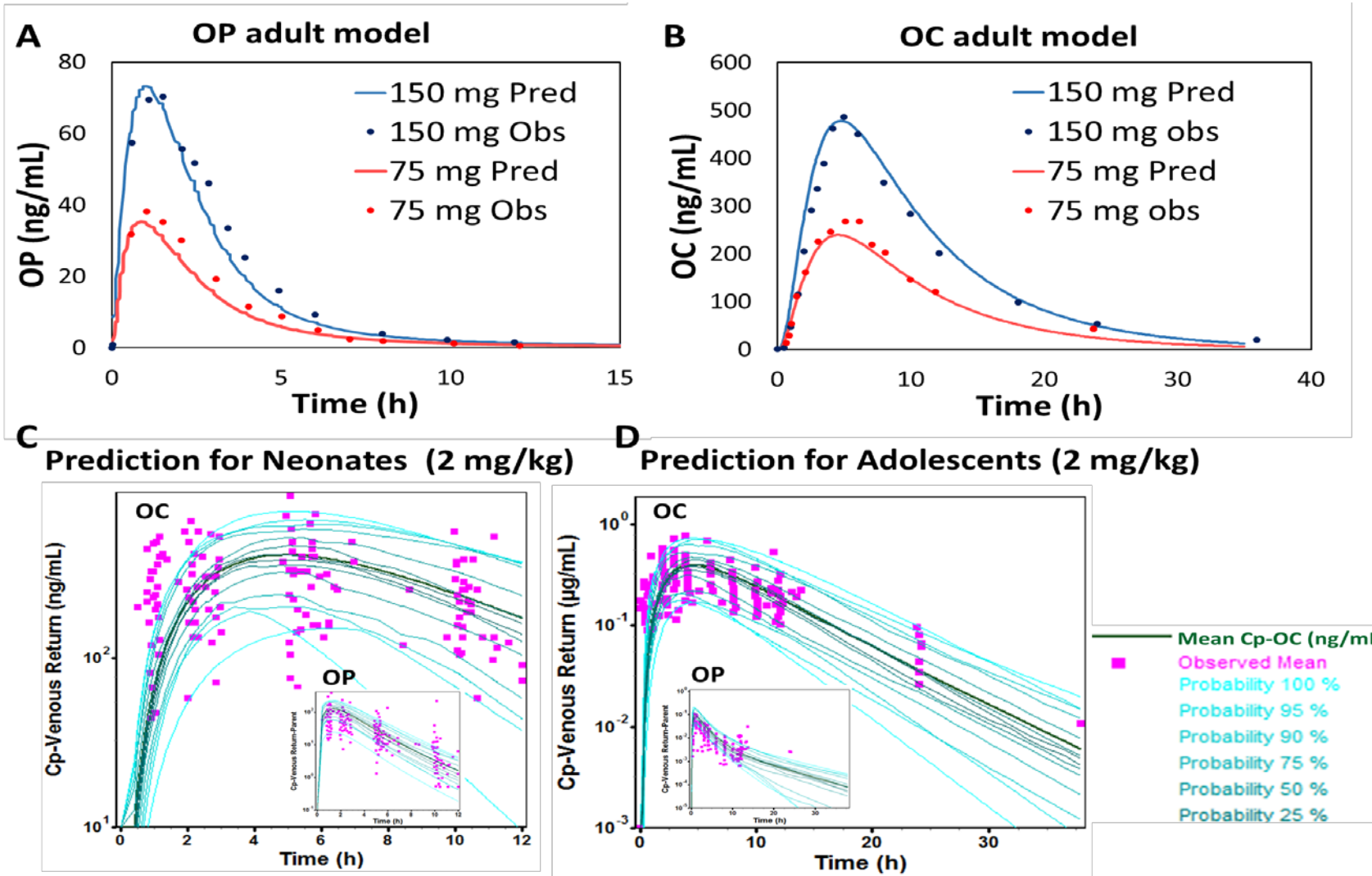
- Physiology change: predicted using Age-related PEAR™ and ACAT™ module
- Drug-dependent parameters: from adult model
- CES1 and renal clearance (OC) were changed

c. Pediatric & Adult Model Application

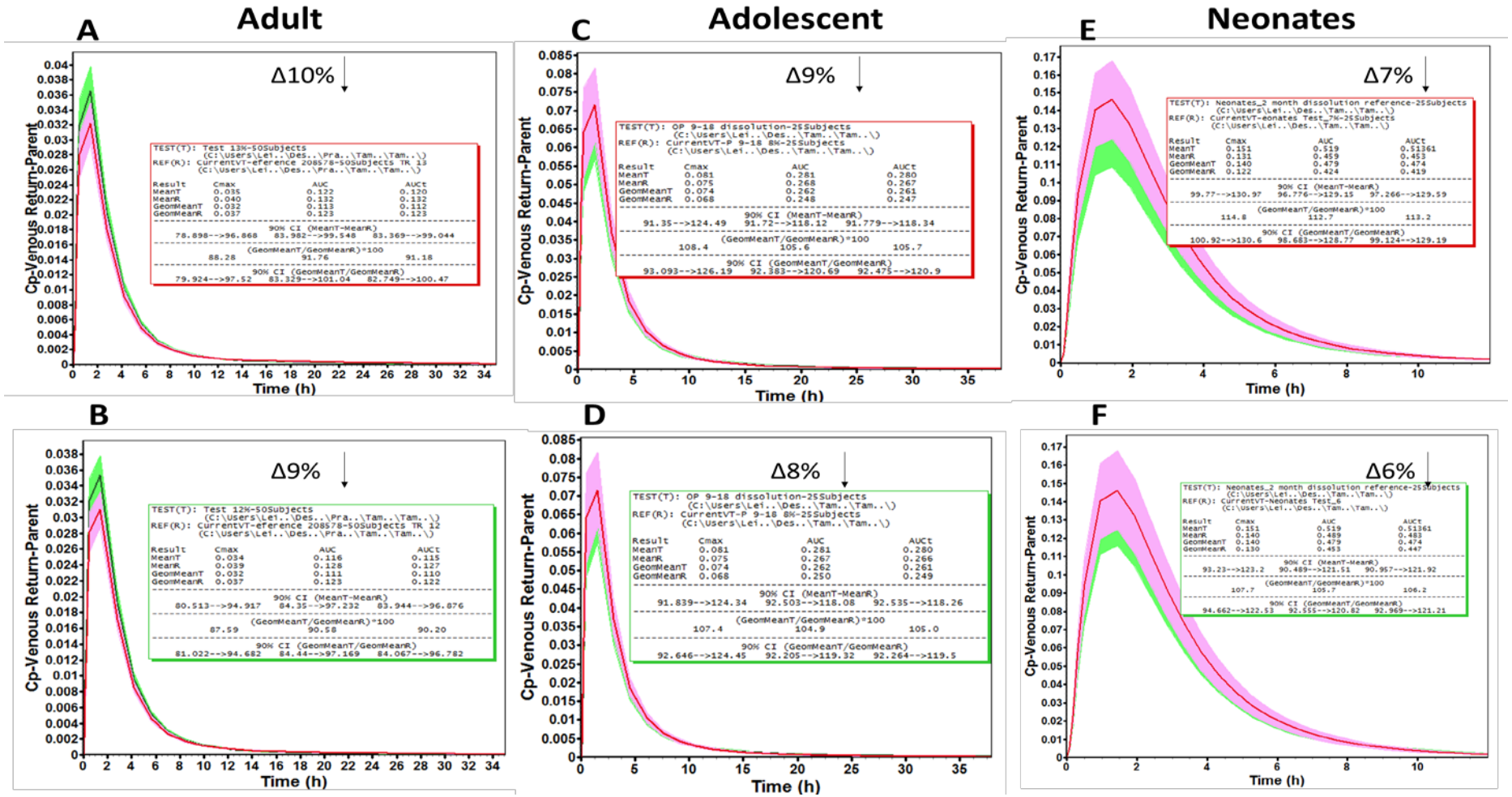
- Virtual BE performed to evaluate generic products and set clinically relevant specifications

Oseltamivir (OP, Tamiflu®), an ester prodrug of the antiviral molecule oseltamivir carboxylate (OC), **Poster M1430-13-84**

Simulated and Observed Concentration Time Profiles for OP and OC in Adults and Pediatrics



Population and Virtual BE Analysis between Reference Products in Adults and Pediatrics to Determine "Safe Space" of Dissolution for OP



Case Summary

- The virtual BE analysis indicated that drug products with the dissolution boundary at 9% slower than dissolution profile of pivotal bio-batch could maintain BE to RLD in adults.
- In contrast, a stringent trend of dissolution boundary (safe space) was observed for pediatrics (8% slower for 8-18-year-old adolescents, 6% slower for children, infants and neonates).
- This study highlights the utility of PBPK absorption modeling and simulation in prediction of BE and providing a quantitative basis for setting clinical relevant specifications for dissolution for OP in both adults and pediatric populations.

OP: oseltamivir; OC: oseltamivir carboxylate; RLD: reference listed drug

Poster M1430-13-84

Challenges and Opportunities (e.g., When Using PBPK Absorption Model)

Current status

- GI physiology could be incorporated in PBPK model and more understanding is needed on the upper part of GI tract
- Population predictions are generally used in PBPK model
- Drug substance and product attributes such as solubility, permeability, dissolution profiles and particle size are used as model inputs

Further Improvement

- Need further understanding of physiology in the lower part of GI tract, such as colon for drugs that will be absorbed in colon
- Subject variabilities should be considered when needed
- Consistent and adequate approach of generating (biorelevant) solubility, dissolution profiles, permeability and particle size changes during the possible precipitation process is needed

Challenges and Opportunities (e.g., When Using PBPK Absorption Model)

Current status

- Some drug/formulation-dependent or system-dependent parameters are used as model inputs with assumptions
- Validation/verification of PBPK model is conducted before the application of the model

Further Improvement

- Uncertain drug/formulation-dependent or system-dependent parameters need adequate justification
- Sufficient purpose-dependent model validation/verification is needed

Conclusion

- Currently, modeling and simulation tools, e.g., PBPK absorption modeling and simulation (M&S), has been increasingly used in generic drug applications.
- With continuous improvement along with more submissions, PBPK absorption M&S would aid in setting clinically relevant specification, support bioequivalence (BE) evaluation and study design, support high impact applications such as being used as alternative BE approach to ensure safe and effective use of drug products.
- Submit modeling and simulation data and communicate with the Agency at an early stage, e.g., via pre-ANDA meeting, is encouraged.

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